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Endodontic procedures for retreatment of periapical lesions (Review)

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[Intervention Review]

Endodontic procedures for retreatment of periapical lesions

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ABSTRACT

Background

When primary root canal therapy fails, periapical lesions can be retreated with or without surgery. Root canal retreatment is a non-surgical procedure that involves removal of root canal filling materials from the tooth, followed by cleaning, shaping and obturating of the canals. Root-end resection is a surgical procedure that involves exposure of the periapical lesion through an osteotomy, surgical removal of the lesion, removal of part of the root-end tip**,** disinfection and, commonly, retrograde sealing or filling of the apical portion of the remaining root canal. This review updates one published in 2008.

Objectives

To assess effects of surgical and non-surgical therapy for retreatment of teeth with apical periodontitis.

To assess effects of surgical root-end resection under various conditions, for example, when different materials, devices or techniques are used.

Search methods

We searched the following electronic databases: the Cochrane Oral Health Trials Register (to 10 February 2016), the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 1), MEDLINE Ovid (1946 to 10 February 2016) and Embase Ovid (1980 to 10 February 2016). We searched the US National Registry of Clinical Trials (ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform for ongoing trials (to 10 February 2016). We placed no restrictions regarding language and publication date. We handsearched the reference lists of the studies retrieved and key journals in the field of endodontics.

Selection criteria

We included randomised controlled trials (RCTs) involving people with periapical pathosis. Studies could compare surgery versus non-surgical treatment or could compare different types of surgery. Outcome measures were healing of the periapical lesion assessed after one-year follow-up or longer; postoperative pain and discomfort; and adverse effects such as tooth loss, mobility, soft tissue recession, abscess, infection, neurological damage or loss of root sealing material evaluated through radiographs.

Data collection and analysis

Two review authors independently extracted data from included studies and assessed their risk of bias. We contacted study authors to obtain missing information. We combined results of trials assessing comparable outcomes using the fixed-effect model, with risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, and 95% confidence intervals (CIs). We used generic inverse variance for split-mouth studies.

Main results

We included 20 RCTs. Two trials at high risk of bias assessed surgery versus a non-surgical approach: root-end resection with root-end filling versus root canal retreatment. The other 18 trials evaluated different surgical protocols: cone beam computed tomography (CBCT) versus periapical radiography for preoperative assessment (one study at high risk of bias); antibiotic prophylaxis versus placebo (one study at unclear risk); different magnification devices (loupes, surgical microscope, endoscope) (two studies at high risk); types of incision (papilla base incision, sulcular incision) (one study at high risk and one at unclear risk); ultrasonic devices versus handpiece burs (one study at high risk); types of root-end filling material (glass ionomer cement, amalgam, intermediate restorative material (IRM), mineral trioxide aggregate (MTA), gutta-percha (GP), super-ethoxy benzoic acid (EBA)) (five studies at high risk of bias, one at unclear risk and one at low risk); grafting versus no grafting (three studies at high risk and one at unclear risk); and low energy level laser therapy versus placebo (irradiation without laser activation) versus control (no use of the laser device) (one study at high risk).

There was no clear evidence of superiority of the surgical or non-surgical approach for healing at one-year follow-up (RR 1.15, 95% CI 0.97 to 1.35; two RCTs, 126 participants) or at four- or 10-year follow-up (one RCT, 82 to 95 participants), although the evidence is very low quality. More participants in the surgically treated group reported pain in the first week after treatment (RR 3.34, 95% CI 2.05 to 5.43; one RCT, 87 participants; low quality evidence).

In terms of surgical protocols, there was some inconclusive evidence that ultrasonic devices for root-end preparation may improve healing one year after retreatment, when compared with the traditional bur (RR 1.14, 95% CI 1.00 to 1.30; one RCT, 290 participants; low quality evidence).

There was evidence of better healing when root-ends were filled with MTA than when they were treated by smoothing of orthograde GP root filling, after one-year follow-up (RR 1.60, 95% CI 1.14 to 2.24; one RCT, 46 participants; low quality evidence).

There was no evidence that using CBCT rather than radiography for preoperative evaluation was advantageous for healing (RR 1.02, 95% CI 0.70 to 1.47; one RCT, 39 participants; very low quality evidence), nor that any magnification device affected healing more than any other (loupes versus endoscope at one year: RR 1.05, 95% CI 0.92 to 1.20; microscope versus endoscope at two years: RR 1.01, 95% CI 0.89 to 1.15; one RCT, 70 participants, low quality evidence).

There was no evidence that antibiotic prophylaxis reduced incidence of postoperative infection (RR 0.49, 95% CI 0.09 to 2.64; one RCT, 250 participants; low quality evidence).

There was some evidence that using a papilla base incision (PBI) may be beneficial for preservation of the interdental papilla compared with complete papilla mobilisation (one RCT (split-mouth), 12 participants/24 sites; very low quality evidence). There was no evidence of less pain in the PBI group at day 1 post surgery (one RCT, 38 participants; very low quality evidence).

There was evidence that adjunctive use of a gel of plasma rich in growth factors reduced postoperative pain compared with no grafting (measured on visual analogue scale: one day postoperative MD -51.60 mm, 95% CI -63.43 to -39.77; one RCT, 36 participants; low quality evidence).

There was no evidence that use of low energy level laser therapy (LLLT) prevented postoperative pain (very low quality evidence).

Authors' conclusions

Available evidence does not provide clinicians with reliable guidelines for treating periapical lesions. Further research is necessary to understand the effects of surgical versus non-surgical approaches, and to determine which surgical procedures provide the best results for periapical lesion healing and postoperative quality of life. Future studies should use standardised techniques and success criteria, precisely defined outcomes and the participant as the unit of analysis.

PLAIN LANGUAGE SUMMARY

Procedures for retreatment of failed root canal therapy

Review question

We aimed to find out the best way to retreat patients for whom root canal therapy has failed. We wanted to know whether surgical or non-surgical retreatment was better, and if using specific materials, devices or procedures in surgery might improve healing of the lesion or reduce patient discomfort after surgery. This review updates one published in 2008.

Background

In root canal therapy, the infected pulp of a tooth is removed, and the root cavity is disinfected and filled with a sealing material. However, if micro-organisms that caused the infection are not completely removed, after some time they may cause a disease at the tip of the root, called a periapical lesion. Treatment for this requires a second intervention, which can be performed in the same way as the first treatment, from the crown into the root canal, to remove the existing filler and clean and disinfect as well as possible before sealing again. Alternatively, should this procedure fail, or if it is not feasible, a surgical intervention can be used.

Study characteristics

We conducted a wide search of medical and dental literature up to 10 February 2016. We identified 20 studies that randomised participants to groups receiving different forms of retreatment of periapical lesions. These studies evaluated nine different comparisons: surgical versus non-surgical treatment (two studies, one monitoring participants for up to 10 years); two diagnostic radiographic techniques (one study); the occurrence of postoperative infection with or without antibiotics (one study); use of different devices for enhancing the surgeon's view during the most critical steps of the surgical procedure (one study); the aesthetic appearance of the gum next to the treated tooth and pain after operation when two different types of gingival incision were used (two studies); use of minimally invasive ultrasonic devices or traditional rotating burs to manage the tip of the root (one study); use of different materials for filling the root-end (seven studies); filling of the periapical lesion with a grafting material (four studies); and exposure of the surgical site to a low energy level laser to reduce pain (one study).

Key results

There is no evidence that a surgical approach leads to better results compared with non-surgical retreatment at one year (or at four or 10 years) after intervention. However, people treated surgically reported more pain and swelling during the first week after treatment.

Different surgical techniques were evaluated. Healing at one-year follow-up seemed to be improved by use of ultrasonic devices, instead of the traditional bur, for root-end preparation. There was some evidence of better healing at one-year follow-up when root-ends were filled with mineral trioxide aggregate compared with their being treated by smoothing of orthograde gutta percha root filling.

Use of a graft composed of a gel enriched with the patient's own platelets applied to the defect during the surgical procedure significantly reduced postoperative pain. Exposure to a low energy level laser did not apparently reduce pain at the surgical site.

A small gingival incision may preserve the gum between two adjacent teeth, improving the aesthetic appearance and causing less pain after surgery.

There was no evidence that use of antibiotics reduces the occurrence of postoperative infection (although when the procedure is done well, infection is an extremely rare event).

Different ways of enhancing the surgeon's view did not lead to different results at least one year after operation, and results of retreatment were independent of the radiographic technique used to make the diagnosis.

Quality of the evidence

We judged the quality of the evidence to be poor; therefore we cannot rely on the findings. Only one study was at low risk of bias;we judged the majority to be at high risk of bias.

Author conclusions

It is difficult to draw conclusions, as the evidence currently available is of low to very low quality. More randomised controlled trials conducted to high standards are needed to find out the effects of the surgical versus non-surgical approach and, when surgery is used, which materials, devices or operative protocols are best for improving lesion healing and reducing patient discomfort.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Root-end resection versus root canal retreatment

Patient or population: people requiring retreatment of periapical lesions
Setting: university clinics
Intervention: root-end resection (with root-end filling)
Comparison: root canal retreatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with root canal re-treatment	Risk with root-end re-section and filling				
Healing - 1 year	726 per 1000	835 per 1000 (704 to 980)	RR 1.15 (0.97 to 1.35)	126 (2 RCTs)	⊕◯◯◯ **very low**[a,b,c]	RR after 4 years was 1.03 (0.89 to 1.20) (1 study, 82 participants) RR after 10 years was 1.11 (0.88 to 1.41) (1 study, 95 participants)
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	279 out of 1000	932 out of 1000 (572 to 1515)	RR 3.34 (2.05 to 5.43)	87 (1 study)	⊕⊕◯◯ **low**[d]	Number of participants reporting pain each day in the first postoperative week was significantly higher in the surgical group than in the non-surgical group
Occurrence of postoperative infection - 4 weeks	Not assessed					

Height loss of interdental papilla	Not assessed
Maximum pain assessed with verbal rating scale (VRS)	Not assessed

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Quality of evidence was downgraded owing to heterogeneity (inconsistency).
[b] Quality of evidence was downgraded owing to imprecision (CI includes RR of 1.0).
[c] Quality of evidence was downgraded because both studies had high risk of bias.
[d] Quality of evidence was downgraded because it was based on a single small study at high risk of bias.

BACKGROUND

Description of the condition

Root canal treatment for the infected pulp of a tooth aims to eradicate pathological microbiota and prevent future infection within the root canals. Root canal treatment should obtain proper root canal shape, so an efficient cleaning can be performed before three-dimensional filling (Wesselink 2010). In recent years, the number of people seeking root canal treatment has dramatically increased because a conservative approach is preferred over tooth extraction (Azarpazhooh 2013a; Azarpazhooh 2013b).

Even when an adequate standard of treatment is performed, failures may occur, owing to the anatomical characteristics of the root canal system and to the presence of peculiar noxious factors within the inflamed tissue (Nair 2004; Nair 2006). The persistence of micro-organisms in the root canal system may induce an inflammatory and immune response in the periradicular (periapical) tissues, resulting in local bone destruction. Furthermore, contamination of the periradicular tissues and of the filling material by micro-organisms may initiate a foreign body reaction, thereby impairing tissue healing.

Large cross-sectional studies from different countries have reported that the prevalence of apical periodontitis and other post-treatment periradicular disease can exceed 30% of all root-filled teeth (Boucher 2002; Friedman 2002; Peters 2011; Tavares 2009), suggesting a considerable need for treatment of this condition.

Although two-dimensional imaging techniques have been used in the past, it has been proposed that three-dimensional imaging delineates greater detail, especially in the periradicular tissues. This may impact the diagnosis of periapical lesions requiring treatment, although robust evidence is lacking (Horner 2013; Petersson 2012).

Furthermore, the presence of cysts, extraradicular infections or other conditions not properly related to a dental pathosis, such as foreign body reactions, could be an indication for root-end resection.

Description of the intervention

Although success rates up to 97% have been reported for the initial root canal treatment (Friedman 2002), failure may occur after treatment, mainly owing to incomplete removal of the pathogenic microbiota. In cases of persistent apical periodontitis or another post-treatment periapical disease in a previously treated tooth, as a consequence of the failure of primary root canal treatment to permanently eradicate the infection, two possible treatment alternatives exist to preserve the tooth: root canal retreatment and root-end resection.

Root canal retreatment has the same aim as primary treatment of infected root canals: complete elimination of micro-organisms and hermetic sealing with biocompatible materials. This is accomplished by removal of root canal filling material, disinfection of the root canal system and sealing of root canals (Machtou 2010). However, when root canal retreatment is not feasible, when it fails, when it is unlikely that it can improve on the previous result or when biopsy of the periapical lesion is necessary, a surgical intervention consisting of root-end resection with or without root-end filling might be indicated and represents the last chance for avoiding tooth extraction.

Root-end resection (also named endodontic surgery, periradicular surgery, periapical/apical surgery or apicoectomy) consists of surgical removal of a periapical lesion, resection of the apical portion of the root, disinfection and sealing of the apical portion of the remaining root canal (Gutmann 1991).

Standard root-end resection is performed through an osteotomy to make the site of the lesion accessible. Then, the technique includes surgical debridement of the pathological periradicular tissue, bevel resection of the apex with a bur, root-end preparation and placement of root-end filling material to seal the root canal. In the past, amalgam was generally used as the root filling material (Gutmann 1991).

A modern approach to root-end resection involves the use of magnification to allow a smaller osteotomy. In addition, the apex is resected with minimal or no bevel and the root-end is treated with ultrasonic tips, then is sealed with modern root-end filling materials other than amalgam (Kim 2006; Tsesis 2006). This approach combines modern ultrasonic preparation and filling materials with use of microsurgical instruments, high-power magnification and illumination to overcome the limitations associated with standard root-end resection, achieving a higher probability of success (Setzer 2010). The microscopic approach to root-end resection ensures easier root apex identification; also, the resected root apices can disclose, under magnification and illumination, complicated anatomical characteristics, intricate details of the apical ramifications, and isthmuses, microfractures and additional canals, allowing proper disinfection and filling of all root canals. Furthermore, the ultrasonic instruments used together with the microscope ensure that root-end preparation may be performed in a conservative, deep and coaxial way, and that the root-end filling may be precisely accomplished (Kim 2006; Setzer 2010).

Various protocols have been proposed to optimise the results of root-end resection and to reduce patient discomfort. For example, guided tissue regeneration with the use of membranes has been applied, different root-end fillers have been used and different bone substitutes for enhancing bone regeneration have been adopted (Gutmann 2014).

Soft tissue management during root-end resection was improved by the introduction of microsurgical instruments. Adequate soft tissue preservation has a beneficial impact on patient-related outcomes during the early postoperative period, on postsurgical aesthetic outcomes and on healing (Kim 2006; Taschieri 2014; Taschieri 2016; Velvart 2005).

In a small segment of failed root canal cases, root canal retreatment or root-end resection is not feasible or impractical. One alternative is intentional replantation, which is a procedure in which the tooth is gently extracted, curettage of the apical lesion (when present) is performed, the apicoectomy and root-end filling procedure are performed extraorally and the tooth is replanted in its alveolar socket. Minimal extraction trauma and very short extraoral time (less than 10 minutes) are the most critical factors contributing to the success of this procedure, which has strict selection criteria for applicability. Its success rate, however, has been reported to be far lower than that of root canal retreatment or root-end resection (Bender 1993; Rouhani 2011).

Another alternative to performing any kind of immediate operative treatment is to just observe and recall for further assessment. The possibility always exists that a periapical lesion that emerges or persists following root canal treatment may heal spontaneously. This option requires the patient agrees with the plan to not intervene and accepts undergoing an observation period of unpredictable duration to follow the natural history of the lesion. Of course, in case of painful exacerbation of the disease (flare-ups), a decision to treat can be made, although it has been reported that the risk of flare-ups among persistent lesions is very rare, and that they have minimal impact on daily activities (Yu 2012).

How the intervention might work

Root canal retreatment has the main aim of removing resident bacteria from the root canal systems and avoiding recurrence of intracanal infection.

After the root canal is accessed through an opening in the crown, and crowns, bridges or posts are removed, the root filling material has to be removed. Root canals then are reshaped, irrigated with antimicrobial solution to ensure complete eradication of microorganisms and closed with proper root canal filling material. Finally, the access hole is sealed (Machtou 2010; Ruddle 2004).

Root-end resection with or without root-end filling aims to regenerate damaged periapical tissues, confine intracanal bacteria and excise the lesion itself (Nair 2006; Von Arx 2001).

Complete surgical removal of the periapical lesion, adequate resection of the apex, root-end preparation and three-dimensional retrograde filling and sealing of the so-created root-end cavity are necessary to allow periapical tissue healing, which consists of neoosteogenesis in the cavity created by the lesion (Gutmann 1991).

Why it is important to do this review

Cochrane Oral Health undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of clinically important titles to be maintained in *The Cochrane Library* (Worthington 2015). The operative and prosthodontic dentistry expert panel identified this review as a priority title (Cochrane OHG priority review portfolio).

Evidence of whether to use root canal retreatment or root-end resection, in the case of a primary root canal treatment failure, is scarce and is now out of date (Del Fabbro 2007; Torabinejad 2009). Therefore, assessment of clinical and radiographic outcomes of these two treatment options is necessary to compare their success rates and to determine whether differences between them can be identified, with the final aim of providing clinicians with up-to-date information about current RCT evidence.

Furthermore, owing to variability in proposed techniques and heterogeneity in study design evident in the available literature, we seek to understand how root-end resection protocols work, and which variables may affect clinical outcomes (Setzer 2010; Setzer 2012). We will systematically evaluate the efficacy of modern techniques to justify their use as a reliable alternative to standard surgical protocols.

OBJECTIVES

To assess effects of surgical and non-surgical therapy for retreatment of teeth with apical periodontitis.

To assess effects of surgical root-end resection under various conditions, for example, when different materials, devices or techniques are used.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials dealing with root canal retreatment of teeth presenting periapical pathosis.

Types of participants

People who have had endodontic treatment of root canals of one or more teeth and who were diagnosed with a periapical condition requiring retreatment.

Types of interventions

Interventions for retreatment of teeth with periapical pathosis, consisting of one of the following.

- Root canal retreatment.
- Root-end resection following a standard protocol (i.e. without magnification devices and with a bur for apex resection

and root-end preparation, a long bevel and amalgam as filling material).

- Root-end resection following a modern protocol (i.e. use of magnification devices with root-end preparation through ultrasonic tips, a short bevel and modern sealing materials).

Types of outcome measures

We were interested in the healing of the periapical lesion (assessed clinically and radiologically), the occurrence of adverse effects and the impact of the intervention on postoperative quality of life.

Primary outcomes

- One-year healing of periapical pathosis evaluated by assessment of clinical signs and symptoms (absence of pain, suppuration, swelling) and through two-dimensional or three-dimensional radiological examination
- Absence or presence of adverse effects or unexpected sequelae after endodontic surgery (tooth loss, mobility, soft tissue recession, abscess, infection, neurological damage, loss of root sealing material evaluated through radiographs)
- Patient-reported outcomes such as postoperative pain and discomfort or completion of an appropriate quality of life measurement during the first week after surgery

Secondary outcomes

- Longer than one-year healing of the periapical pathosis evaluated by assessment of clinical signs and symptoms (absence of pain, suppuration, swelling) and through radiological examination.

Search methods for identification of studies

To identify studies for this review, we developed detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE (Ovid) and were revised appropriately for each database. The search strategy used a combination of controlled vocabulary and free-text terms and was linked with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying RCTs in MEDLINE: sensitivity-maximising version (2008 revision), as referenced in Chapter 6.4.11.1 and detailed in Box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Lefebvre 2011). We provide details of the MEDLINE search in Appendix 1. The search of Embase was linked to the Cochrane Oral Health filter for identifying RCTs.

Electronic searches

We searched the following electronic databases.

- Cochrane Oral Health Trials Register (searched 10 February 2016) (see Appendix 2).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 1), in *The Cochrane Library* (searched 10 February 2016) (see Appendix 3).
- MEDLINE Ovid (1946 to 10 February 2016) (see Appendix 1).
- Embase Ovid (1980 to 10 February 2016) (see Appendix 4).

We applied no restrictions on language or date of publication in our searches of electronic databases.

Searching other resources

We searched the following trial registries for ongoing studies.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (http://clinicaltrials.gov/; searched 10 February 2016).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 10 February 2016).

We searched the reference lists of included studies and of relevant systematic reviews for additional studies.
Moreover, we performed a handsearch of all issues (from 1960 to February 2016) of the following journals.

- *British Journal of Oral and Maxillofacial Surgery.*
- *International Endodontic Journal.*
- *Journal of Endodontics.*
- *Dental Traumatology* (formerly *Dental Traumatology and Endodontics*).
- *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics.*
- *International Journal of Oral and Maxillofacial Surgery.*
- *Journal of Oral and Maxillofacial Surgery.*
- *Australian Endodontic Journal.*
- *British Dental Journal.*
- *Australian Dental Journal.*
- *Journal of Dentistry.*

To identify additional unpublished and ongoing RCTs, we contacted manufacturers of instruments for root canal treatment and for endodontic surgery, along with the authors of selected RCTs.

Data collection and analysis

Selection of studies

Two review authors (SC, MDF) independently screened titles and abstracts of the retrieved studies and discarded non-relevant articles. We obtained the full text of all studies that we considered relevant, or for which we did not have sufficient information, and two review authors (SC, MDF) independently evaluated these to

check whether they met the inclusion criteria. The two review authors resolved disagreements by discussion and consultation with a third review author. We collated multiple publications of the same study. For all studies rejected at this stage, we recorded reasons for exclusion in the Characteristics of excluded studies tables.

Data extraction and management

Two review authors (SC, IT) independently extracted data and resolved disagreements through discussion and consultation with a third review author. In cases of missing information, we contacted authors of the included studies through email. In cases of missing or incomplete data and absence of further clarification by study authors, we excluded these reports from the analysis.

We recorded the following data for each included study.

- Demographic characteristics of the study population.
- Setting, country, year, study design.
- Funding source.
- Number of surgeons involved.
- Characteristics of the intervention.
- Outcome characteristics (how outcomes were assessed, time intervals, results).

Assessment of risk of bias in included studies

Two review authors (IT, PSB) independently assessed the risk of bias of included studies. If papers to be assessed listed one or more review authors on the byline, review authors not involved in the trial independently evaluated these studies. We resolved disagreements by discussion.

We conducted the risk of bias assessment according to instructions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We considered five items for each study: selection bias, performance bias, detection bias, attrition bias and reporting bias. For each domain, we judged the risk as low, unclear or high. If a study had low risk for each item, we judged that study to have low risk of bias. If a study had unclear risk for at least one domain but no items scored at high risk, we judged that study to have unclear risk of bias. If a study had high risk of bias for at least one domain, we judged that study to be at high risk of bias.

Measures of treatment effect

For dichotomous outcomes, we calculated estimates of effects of interventions as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous variables, we calculated estimates of effects of interventions as mean differences (MDs) with 95% CIs.

Unit of analysis issues

In parallel-group studies, the statistical unit of analysis was usually the participant - not the lesion or the tooth. We undertook a tooth-based meta-analysis if only tooth-based data - instead of participant-based data - were available for all studies addressing a given comparison. In split-mouth studies, the tooth was considered as the unit of analysis.

Dealing with missing data

When necessary, we contacted corresponding authors of study articles through email to request missing data regarding specific items considered in the risk of bias assessment. If these authors did not respond, we sent the same email again, copying in coauthors, a maximum of three times. If no answer was obtained, and no sufficient outcome data were available for the analysis, we did not include the data in the analysis and considered the relative item at high risk of bias.

Assessment of heterogeneity

We assessed heterogeneity among studies using the Chi^2 test, considering significance at $P < 0.1$. We quantified heterogeneity by calculating I^2 statistics. If I^2 was over 50%, we considered it significant (Higgins 2011).

Assessment of reporting biases

We assessed publication bias by testing for funnel plot asymmetry, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If asymmetry was evident, we investigated this and described possible causes.

Data synthesis

We performed meta-analysis for studies with comparable outcomes, calculating RRs for dichotomous data ('success' or 'non-success' of retreatment) and MDs for continuous data (self-reported pain on a visual analogue scale). As in the previous version of this review, we dichotomised data regarding healing of the periapical lesion that are usually expressed as four scores (complete, incomplete, uncertain, unsatisfactory healing) into success (complete plus incomplete healing data) and non-success (uncertain plus unsatisfactory healing data). Similarly, for other outcomes expressed as scores composed of four or five items, we grouped those that were similar in order to express data in a dichotomous form and allow meta-analysis. We used the fixed-effect model, as each meta-analysis included fewer than four studies. For data from split-mouth studies, we used the generic inverse variance method. We had planned to calculate numbers needed to treat for the primary outcome. When meta-analysis was not appropriate, we described individual study data in the text.

We used the software Review Manager for meta-analysis computations (RevMan 5.3).

Subgroup analysis and investigation of heterogeneity

We had planned to perform subgroup analysis when we identified a sufficient number of included studies. We had planned subgroups based on:

- whether root-end resection was performed with a standard or a modern technique;
- whether or not guided bone regeneration (GBR) techniques were applied;
- use of different magnification devices (surgical microscope, loupes, endoscope); and
- use of different root-end fillers (such as mineral trioxide aggregate (MTA), ethoxy benzoic acid (EBA) cement and intermediate restorative material (IRM)).

Sensitivity analysis

We had planned to perform sensitivity analysis by excluding studies at high risk of bias to evaluate the effect of study risk of bias on overall effects.

Assessment of quality of the evidence

We assessed the quality of the body of evidence using GRADE criteria, with reference to the overall risk of bias of included studies, directness of the evidence, consistency of the results, precision of the estimates and risk of publication bias. We graded the quality of the body of evidence for each primary outcome as high, moderate, low or very low.

Presentation of main results

We developed a 'Summary of findings' table for each comparison and for the primary outcomes of this review using GRADEPro software. We reported the following outcomes.

- Healing at one year.
- Pain (visual analogue scale 0 to 100) on day 1.
- Prevalence of pain.
- Occurrence of postoperative infection.
- Loss of interdental papilla height.

RESULTS

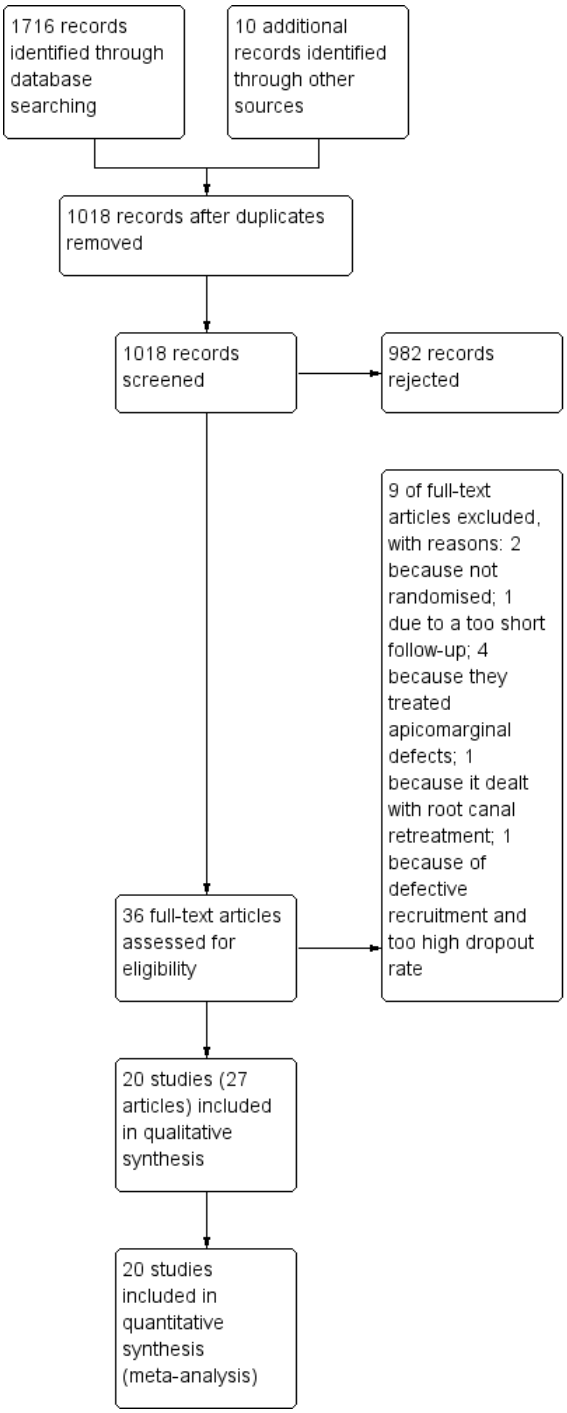
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We present the flow of the article screening process in Figure 1. The electronic search yielded a total of 1716 records. After deduplication, 1018 records remained. After screening of titles and abstracts, we considered 26 articles potentially eligible for inclusion. We selected 10 additional articles by journal handsearching or by searching through the references of the selected articles. After full-text evaluation, we excluded nine studies (Bader 1998; Dhiman 2015; Garrett 2002; Goyal 2011; Huumonen 2003; Kim 2008; Marin-Botero 2006; Shearer 2009; Von Arx 2010a) and included 20 studies (27 publications) (Angerame 2015; Chong 2003; Christiansen 2009; Danin 1996; De Lange 2007; Del Fabbro 2009; Del Fabbro 2012; Kurt 2014; Kvist 1999; Lindeboom 2005a; Lindeboom 2005b; Payer 2005; Pecora 2001; Song 2012; Taschieri 2007; Taschieri 2008; Velvart 2004; Walivaara 2009; Walivaara 2011; Zetterqvist 1991). Seven of the included studies (Chong 2003; Christiansen 2009; Kvist 1999; Taschieri 2007; Taschieri 2008; Velvart 2004; Zetterqvist 1991) were reported in multiple articles.

Figure 1. Study flow diagram



Included studies

Of the 20 included studies, five were performed in Sweden (Danin 1996; Kvist 1999; Walivaara 2009; Walivaara 2011; Zetterqvist 1991), six in Italy (Angerame 2015; Del Fabbro 2009; Del Fabbro 2012; Pecora 2001; Taschieri 2007; Taschieri 2008), three in The Netherlands (De Lange 2007; Lindeboom 2005a; Lindeboom 2005b) and one each in Austria (Payer 2005), Denmark (Christiansen 2009), Korea (Song 2012), Switzerland (Velvart 2004), Turkey (Kurt 2014) and United Kingdom (Chong 2003).

Characteristics of study design, trial setting and investigators

All studies except Velvart 2004 used a parallel-group study design. Velvart 2004, the only split-mouth study, evaluated the height of interdental papilla after root-end resection, comparing two different approaches for incision: papilla base incision (PBI) versus complete papilla mobilisation, involving the two papillae adjacent to the tooth undergoing endodontic surgery.

One trial declared that support was received from industry directly involved in the product being tested, along with free material (De Lange 2007). For four studies, funding was provided by the author's institution (Chong 2003; Christiansen 2009; Danin 1996; Lindeboom 2005a). Six studies declared that no specific funding was received for performing the study (Del Fabbro 2009; Del Fabbro 2012; Kvist 1999; Lindeboom 2005b; Taschieri 2007; Taschieri 2008). For the remaining nine studies (Angerame 2015; Kurt 2014; Payer 2005; Pecora 2001; Song 2012; Velvart 2004; Walivaara 2009; Walivaara 2011; Zetterqvist 1991), study authors did not state the source of funding (if any) and provided no information.

Seven studies included only one surgeon (Angerame 2015; Christiansen 2009; Del Fabbro 2009; Del Fabbro 2012; Kurt 2014; Kvist 1999; Song 2012); 10 studies included two surgeons (Chong 2003; Danin 1996; Lindeboom 2005a; Pecora 2001; Taschieri 2007; Taschieri 2008; Velvart 2004; Walivaara 2009; Walivaara 2011; Zetterqvist 1991); one study had three surgeons (Lindeboom 2005b); one study had four surgeons Payer 2005; and one study had seven surgeons (five oral and maxillofacial surgeons and two endodontic surgeons) (De Lange 2007).

Eight studies reported an a priori sample size calculation (Chong 2003; De Lange 2007; Del Fabbro 2009; Del Fabbro 2012; Kvist 1999; Lindeboom 2005b; Song 2012; Taschieri 2008).

Nine studies did not specify the lesion size (Angerame 2015; Chong 2003; Christiansen 2009; De Lange 2007; Kurt 2014; Song 2012; Velvart 2004; Walivaara 2009; Zetterqvist 1991), although two of these (Christiansen 2009; Kurt 2014) reported that they estimated the lesion condition by using the periapical index (PAI). The other studies reported lesion sizes smaller than 5 mm (Payer 2005); smaller than 5 mm and 5 mm or larger (Danin 1996; Kvist 1999); smaller than 5 mm, 5 to 9 mm and larger than 9 mm (Walivaara 2011); 3 to 19 mm (Taschieri 2008); 8 to 12 mm (Del Fabbro 2012); smaller than 10 mm (Del Fabbro 2009; Lindeboom 2005a; Lindeboom 2005b); and larger than 10 mm (Pecora 2001; Taschieri 2007).

Characteristics of the interventions

The included studies evaluated the following comparisons of different aspects of endodontic surgery.

- Root-end resection with root-end filling versus root canal retreatment of periapical lesions (Danin 1996; Kvist 1999).
- Type of preoperative evaluation: cone beam computed tomography (CBCT) versus conventional periapical radiography (Kurt 2014).
- Prophylactic antibiotic versus placebo (Lindeboom 2005a).
- Incision type: papilla base incision (PBI) versus complete papilla mobilisation (Velvart 2004); PBI versus sulcular incision (Del Fabbro 2009).
- Magnification type: surgical microscope versus endoscope versus surgical loupes (Taschieri 2008).
- Ultrasonic device versus conventional bur for root-end preparation (De Lange 2007).
- Root-end filling material: glass ionomer cement versus amalgam (Zetterqvist 1991); MTA versus IRM (Chong 2003; Lindeboom 2005b); MTA versus gutta-percha smoothing (Christiansen 2009); MTA versus SuperEBA (Song 2012); IRM versus gutta-percha (Walivaara 2009); and IRM versus SuperEBA (Walivaara 2011).
- Grafting versus no grafting: calcium sulphate versus no grafting (Pecora 2001); guided tissue regeneration (GTR) using bovine bone mineral and resorbable collagen membrane versus no GTR (Taschieri 2007); plasma rich in growth factors versus no grafting (Del Fabbro 2012); and platelet-rich fibrin versus no grafting (Angerame 2015).
- Low energy level laser therapy (LLLT) versus placebo versus control (Payer 2005).

Characteristics of outcome measures

The included studies used the following outcomes to assess treatments.

- Periapical healing by clinical and radiographic evaluation, adopting the criteria of Molven 1987 (Angerame 2015; Chong 2003; Song 2012), of Molven 1987 and Rud 1972 (Christiansen 2009; Lindeboom 2005b; Walivaara 2009; Walivaara 2011), of Molven 1987 and Gutmann 1991 (Taschieri 2007; Taschieri

2008), of Zetterqvist 1991 (Kurt 2014; Zetterqvist 1991) and of Reit 1983 (Kvist 1999).

- Periapical healing by radiographic evaluation alone, adopting the criteria of Rud 1972 (Danin 1996; De Lange 2007; Pecora 2001).
- Postoperative pain by visual analogue scale (VAS) (Chong 2003; Christiansen 2009; Del Fabbro 2009; Del Fabbro 2012; Kurt 2014; Kvist 1999; Payer 2005) or by other scales (Angerame 2015).
- Other postoperative symptoms related to patient discomfort, such as swelling, inflammation, bleeding, tenderness on palpation or percussion through a questionnaire that used a Likert scale or other scales (Angerame 2015; Christiansen 2009; Del Fabbro 2009; Del Fabbro 2012; Kurt 2014; Kvist 1999; Payer 2005).
- Assessment of wound healing for signs of infection (Lindeboom 2005a).
- Height of interdental papilla (Velvart 2004).

Duration of follow-up

Follow-ups up to one week were adopted only in studies that aimed to assess postsurgical pain and discomfort and were as follows.

- Two days (Chong 2003).
- Three days (Christiansen 2009).
- Seven days (Angerame 2015; Del Fabbro 2009; Del Fabbro 2012; Kvist 1999; Payer 2005).

Studies assessing healing of periapical lesions reported outcome measures at the following time points.

- One year (Angerame 2015; Christiansen 2009; Danin 1996; De Lange 2007; Kurt 2014; Kvist 1999; Lindeboom 2005b; Pecora 2001; Song 2012; Taschieri 2007; Zetterqvist 1991).
- Two years (Chong 2003; Taschieri 2008).
- Four years (Kvist 1999).
- Five years (Zetterqvist 1991).
- 10 years (Kvist 1999; unpublished data).

Two studies that evaluated healing of periapical lesions reported results in follow-up ranges with a minimum follow-up of 12 months and mean values of 15.6 months (Walivaara 2009) and 13.1 months (Walivaara 2011).

One study evaluated the efficacy of prophylactic antibiotic administration by recording the occurrence of postoperative infection and had a follow-up of four weeks (Lindeboom 2005a).

One study evaluated the height of the interproximal papilla after one-year follow-up (Velvart 2004).

Excluded studies

We excluded two studies because they were not actually randomised to treatment (Bader 1998; Von Arx 2010a). We excluded one study because healing was evaluated after too short a follow-up period (Shearer 2009). We excluded four studies because they treated apicomarginal defects (Dhiman 2015; Goyal 2011; Kim 2008; Marin-Botero 2006); one of which specifically compared the outcome of endodontic microsurgery for apical versus apicomarginal defects (Kim 2008). In the present review, we considered only lesions confined to the periapical region, not endoperiodontal lesions. We excluded one studybecause it dealt only with orthograde endodontic retreatment - not apical surger (Huumonen 2003), and another study because recruitment was defective and the dropout rate was extremely high (Garrett 2002). In that study, recruitment of 60 participants was planned, but only 25 were actually treated and only 13 could be evaluated at the scheduled follow-up.

Risk of bias in included studies

Overall, we judged only one study to be at low risk of bias (Lindeboom 2005b), and four studies to be at unclear risk of bias (Del Fabbro 2009; Lindeboom 2005a; Pecora 2001; Taschieri 2008). We considered all other studies to be at high risk of bias (Angerame 2015; Chong 2003; Christiansen 2009; Danin 1996; Del Fabbro 2012; De Lange 2007; Kurt 2014; Kvist 1999; Payer 2005; Song 2012; Taschieri 2007; Velvart 2004; Walivaara 2009; Walivaara 2011; Zetterqvist 1991). See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

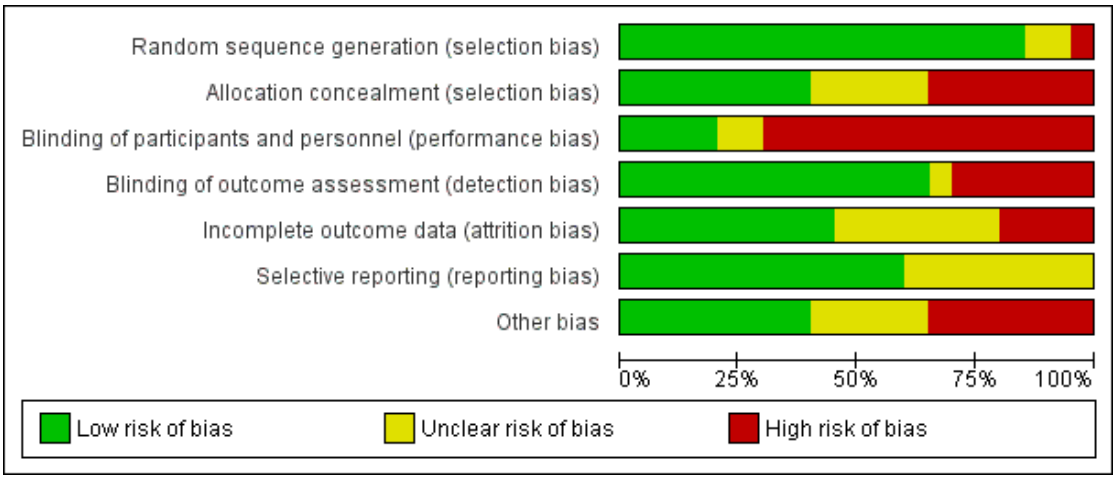
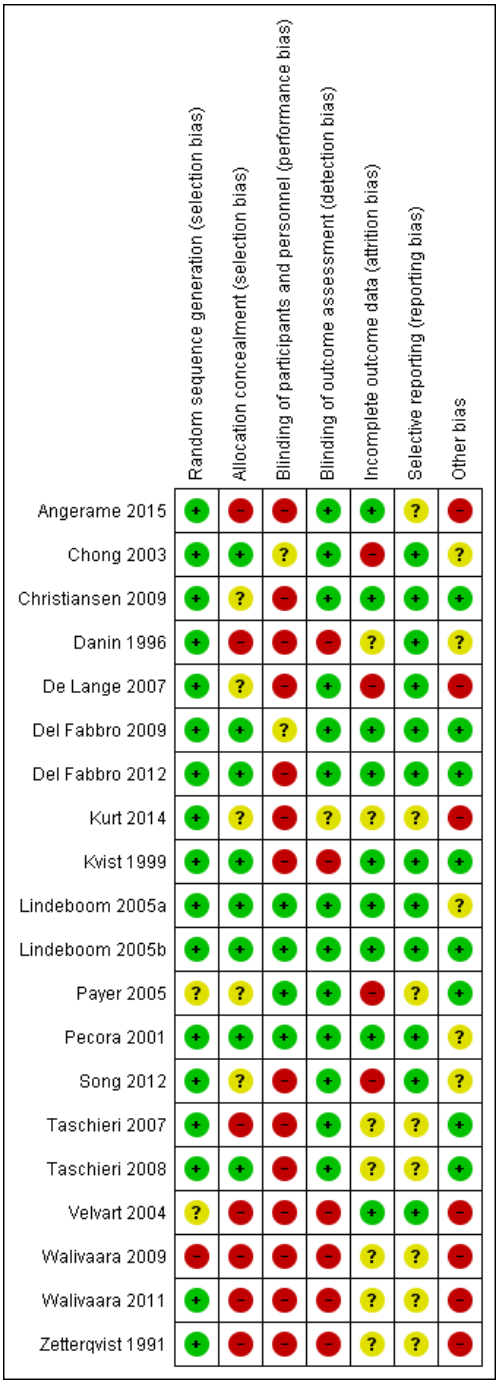


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Random sequence generation

We deemed the randomisation method to be appropriate in 17 studies, and we assessed these studies to be at low risk of bias. Payer 2005 and Velvart 2004 reported no details on the randomisation procedure, and study authors provided no information; we therefore assessed these studies as being at unclear risk of bias. In the study by Walivaara 2009, participants were allocated into two groups according to their date of birth, which meant that we judged this study to be at high risk of bias.

Allocation concealment

When assessing information reported in the trials, we considered allocation concealment as adequate for eight studies (Chong 2003; Del Fabbro 2009; Del Fabbro 2012; Kvist 1999; Lindeboom 2005a; Lindeboom 2005b; Pecora 2001; Taschieri 2008). We considered five trials to have unclear concealment of allocation, even after receiving study authors' replies (Christiansen 2009; De Lange 2007; Kurt 2014; Payer 2005; Song 2012). In seven studies (Angerame 2015; Danin 1996; Taschieri 2007; Velvart 2004; Walivaara 2009; Walivaara 2011; Zetterqvist 1991), allocation concealment, as stated in the article or confirmed by some of the authors, was not attempted and so we assessed these studies as having high risk of bias.

Blinding

Blinding of participants and personnel (performance bias)

In some cases (Danin 1996; Kvist 1999), blinding of treatment to operators or to participants was not feasible, as surgical and non-surgical procedures were compared. In these cases, we classified risk of bias as high. On the basis of information present in the articles and the replies of study authors, we considered the risk of performance bias to be low in five studies (De Lange 2007; Lindeboom 2005a; Lindeboom 2005b; Payer 2005; Pecora 2001), unclear in two studies (Chong 2003; Del Fabbro 2009) and high in 13 studies (Angerame 2015; Christiansen 2009; Danin 1996; Del Fabbro 2012; Kurt 2014; Kvist 1999; Song 2012; Taschieri 2007; Taschieri 2008; Velvart 2004; Walivaara 2009; Walivaara 2011; Zetterqvist 1991).

Blinding of outcome assessment (detection bias)

On the basis of information present in the articles and the replies of trial authors, we judged the risk of detection bias to be low in 13 studies (Angerame 2015; Chong 2003; Christiansen 2009; De Lange 2007; Del Fabbro 2009; Del Fabbro 2012; Lindeboom 2005a; Lindeboom 2005b; Payer 2005; Pecora 2001; Song 2012; Taschieri 2007; Taschieri 2008), unclear in one study (Kurt 2014) and high in six studies (Danin 1996; Kvist 1999; Velvart 2004; Walivaara 2009; Walivaara 2011; Zetterqvist 1991).

Incomplete outcome data

In the study articles, investigators clearly presented adequate information on all participants treated (including reasons for dropout) in nine trials (Angerame 2015; Christiansen 2009; Del Fabbro 2009; Del Fabbro 2012; Kvist 1999; Lindeboom 2005a; Lindeboom 2005b; Pecora 2001; Velvart 2004). This information was only partially reported and remained unclear after the trial author's reply for seven studies (Danin 1996; Kurt 2014; Taschieri 2007; Taschieri 2008; Walivaara 2009; Walivaara 2011; Zetterqvist 1991). For three studies, there was no information at all on dropouts and missing data, which put them at high risk of bias for this item (Chong 2003; Payer 2005; Song 2012). In two studies (De Lange 2007; Zetterqvist 1991), the dropout rate was rather high (> 20%), although investigators provided an explanation for dropouts.

Selective reporting

Thirteen studies reported full information on outcome measures, and we considered these trials to be at low risk of bias (Angerame 2015; Chong 2003; Christiansen 2009; Danin 1996; De Lange 2007; Del Fabbro 2009; Del Fabbro 2012; Kvist 1999; Lindeboom 2005a; Lindeboom 2005b; Pecora 2001; Song 2012; Velvart 2004). Seven studies reported partial or doubtful information on data of outcome measures that were assessed, though they reported the primary outcome healing of the periapical lesion in a satisfactory manner, hence we assessed these studies as being at unclear risk of bias (Kurt 2014; Payer 2005; Taschieri 2007; Taschieri 2008; Walivaara 2009; Walivaara 2011; Zetterqvist 1991). Another reason for the 'unclear' assessment for Payer 2005 was that only diagrams were provided for several variables, making obtaining actual numbers impossible and hence preventing meta-analysis.

Other potential sources of bias

We considered eight studies to be at low risk of any other potential source of bias (Christiansen 2009; Del Fabbro 2009; Del Fabbro

2012; Kvist 1999; Lindeboom 2005b; Payer 2005; Taschieri 2007; Taschieri 2008). Twelve studies did not perform an a priori sample size calculation (Angerame 2015; Christiansen 2009; Danin 1996; Kurt 2014; Lindeboom 2005a; Payer 2005; Pecora 2001; Taschieri 2007; Velvart 2004; Walivaara 2009; Walivaara 2011; Zetterqvist 1991), although this was not per se considered a possible source of bias; we assigned a judgement of 'unclear risk' only when missing sample size calculation was associated with other possible sources of bias. Lindeboom 2005b performed sample size calculation, although investigators did not clearly report the details. In one study (De Lange 2007), comparing two different devices for root-end preparation (ultrasonic device versus round dental bur), seven operators performed surgical procedures; the experience and comparability of the seven operators was not specified, and it was not clear each of them performed interventions in both groups equally; therefore, we judged this study to be at high risk of bias. Other studies failed to give a complete description of the characteristics of the study setting and of participant population (Angerame 2015; Chong 2003; Danin 1996; De Lange 2007; Kurt 2014; Lindeboom 2005a; Payer 2005; Pecora 2001; Song 2012; Velvart 2004; Walivaara 2009; Walivaara 2011; Zetterqvist 1991). We did not consider missing information about study characteristics, such as the recruitment period, sources of funding or participant characteristics including proportion of smokers, age and gender per se as a source of bias, but only as imprecision in reporting. On the other hand, missing information about lesion size and the type of teeth treated (as in Angerame 2015; Chong 2003; De Lange 2007; Pecora 2001; Song 2012; Velvart 2004; Walivaara 2009; and Zetterqvist 1991) may be more relevant as these parameters might affect the treatment outcome and it is important they are equally distributed among groups. In Zetterqvist 1991, which reported one-year and five-year follow-up evaluations, periapical healing was assessed using personal criteria instead of the conventional criteria adopted by most studies. Investigators in the two studies by Walivaara (Walivaara 2009; Walivaara 2011) did not assess participants at a given follow-up time but reviewed them clinically and radiographically after a minimum of one year (12 to 38 months in Walivaara 2009, and 12 to 21 months in Walivaara 2011). Therefore periapical lesion healing was evaluated at a follow-up duration not equal for all teeth. For the quantitative analysis, it was as if all participants were assessed at one year, which was likely to lead to underestimation of the results because some lesions may take longer than one year to heal. We considered the two studies at high risk of bias for this item.

Effects of interventions

See: **Summary of findings for the main comparison** Root-end resection versus root canal retreatment; **Summary of findings 2** Cone beam computed tomography (CBCT) versus periapical radiography; **Summary of findings 3** Preoperative antibiotic prophylaxis versus placebo; **Summary of findings 4** Magnification devices; **Summary of findings 5** Papilla base incision (PBI) incision versus complete mobilisation; **Summary of findings 6** Ultrasonic instruments versus bur; **Summary of findings 7** Root end fillings; **Summary of findings 8** Grafting versus no grafting; **Summary of findings 9** Low energy level laser therapy versus placebo versus control

See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; and Summary of findings 8.

1. Root-end resection with or without root-end filling versus root canal retreatment for secondary treatment of periapical lesions (two trials, 126 participants)

Two studies at high risk of bias addressed this comparison (Danin 1996; Kvist 1999). Kvist 1999 compared surgical and non-surgical treatments at six-month and one-, two- and four-year follow-up periods. The results in the article were summarised only by a diagram but the main author provided us with numerical data that we considered for the present analysis. Danin 1996 provided results for healing at one-year follow-up only. Data from these two studies were dichotomised as described in the Data synthesis section of this review.

We found no clear evidence that surgical intervention had a higher healing rate than non-surgical intervention after one-year follow-up (risk ratio (RR) 1.15, 95% confidence interval (CI) 0.97 to 1.35; Analysis 1.1; Figure 4). We noted heterogeneity between study results (P = 0.02). Similarly, Kvist 1999 found no evidence of a difference in healing rates between root-end resection and root canal retreatment after four years (RR 1.03, 95% CI 0.89 to 1.20; Analysis 1.2; Figure 5). The study author reported that four surgically retreated cases that had been classified as healed at one-year follow-up did show a relapse of the apical radiolucency or presented with clinical symptoms at a later follow-up. The author of the latter study provided us with data recorded at a longer follow-up (10 years, personal communication), which confirmed there was no evidence of a difference between groups (RR 1.11, 95% CI 0.88 to 1.41; Analysis 1.3; Figure 6).

Figure 4. Forest plot of comparison: 1 Root-end resection versus root canal retreatment, outcome: 1.1 Healing - one year

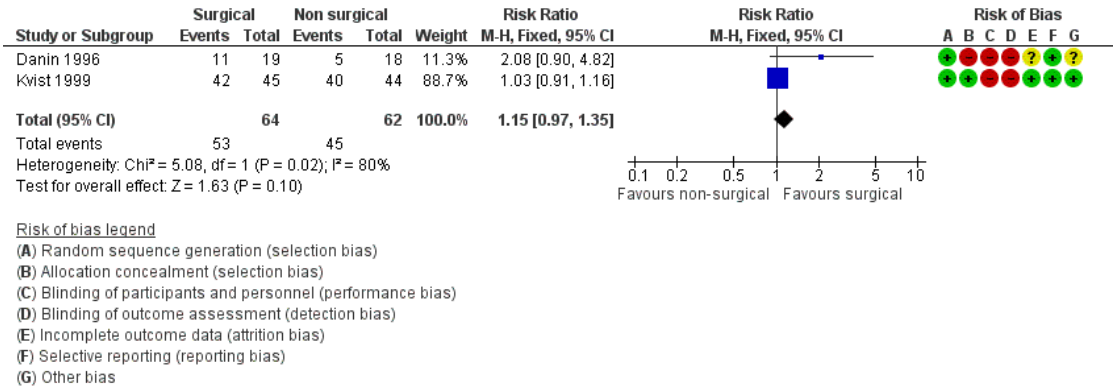
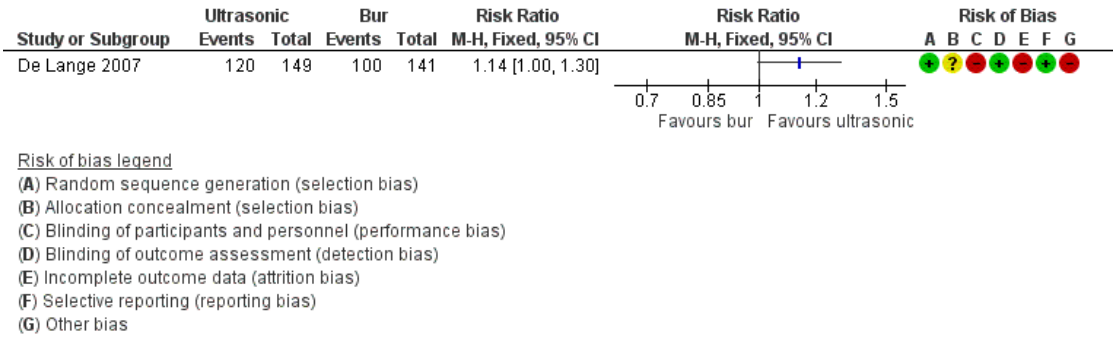


Figure 5. Forest plot of comparison: 6 Ultrasonic versus Bur, outcome: 6.1 Healing - one year



Evaluation of self-reported pain and swelling in the first seven days after secondary treatment showed a significantly higher number of participants reporting pain and swelling in the root-end resection group as compared with the root canal retreatment group (Analysis 1.4; Analysis 1.5).

2. Type of preoperative evaluation: cone beam computed tomography (CBCT) versus conventional periapical radiography (one trial, 39 participants)

One study at high risk of bias addressed this question (Kurt 2014). There was no evidence that use of CBCT in the preoperative evaluation was advantageous, in terms of one-year clinical and radiographic healing, as shown in Analysis 2.1 (RR 1.02, 95% CI 0.70 to 1.47).

3. Antibiotic prophylaxis versus placebo (one trial, 250 participants)

One study at unclear risk of bias addressed this question (Lindeboom 2005a). There was no evidence that use of preoperative antibiotics reduced the incidence of postoperative infection after four weeks compared with placebo, as shown in Analysis 3.1 (RR 0.49, 95% CI 0.09 to 2.64).

4. Magnification devices: surgical microscope versus endoscope versus surgical loupes (one trial, 98 participants/150 teeth)

One study at high risk of bias addressed whether use of magnification devices could bring advantages in clinical and radiographic healing up to two years of follow-up (Taschieri 2008). Results of

this three-arm trial were presented in two articles - one reporting the comparison between surgical loupes and endoscope, after one-year of follow-up, and the other reporting the comparison between surgical microscope and endoscope, at two years of follow-up. Both analyses were tooth-based and showed no evidence of a difference in healing with one or the other magnification device, as shown in Analysis 4.1 (loupes versus endoscope on 71 teeth followed up to one year (RR 1.05, 95% CI 0.92 to 1.20)) and Analysis 4.2 (microscope versus endoscope on 100 teeth followed up to two years (RR 1.01, 95% CI 0.89 to 1.15)).

5. Incision type (two trials, 52 participants)

Two studies addressed the question of whether the type of incision could lead to better results in terms of aesthetics or postoperative quality of life.

One split-mouth study at high risk of bias evaluated the height of interdental papilla after papilla base incision (PBI) versus complete papilla mobilisation techniques (Velvart 2004) at follow-up of one year (12 participants). Results show weak evidence of a lower papilla height reduction with the PBI technique as compared with complete papilla mobilisation after one year (Analysis 5.1; mean difference (MD) -1.04, 95% CI -2.10 to 0.02).

The other study (Del Fabbro 2009), which was at unclear risk of bias, had a parallel design and evaluated pain and postoperative symptoms in participants undergoing PBI versus sulcular incision (complete papilla mobilisation) with follow-up of one week (38 participants). Results showed no evidence of a difference in reported pain on a VAS scale at day one (Analysis 5.2; MD -2.25, 95% CI -7.17 to 2.67; P = 0.37) or day two (MD -1.50, 95% CI -6.34 to 3.34; P = 0.54). On the other hand, there was evidence of less pain in the PBI group than in the sulcular incision group at day 3 (MD -22.00, 95% CI -26.81 to -17.19; P < 0.00001).

6. Ultrasonic device versus conventional bur for root-end preparation (one trial, 290 participants)

One study at high risk of bias addressed this question, evaluating treatment success at one-year follow-up (De Lange 2007). Use of ultrasonic devices for root-end preparation provided weak evidence of an advantage when compared with the traditional bur, as shown by Analysis 6.1 (RR 1.14, 95% CI 1.00 to 1.30). This study adopted the radiographic evaluation criteria of Rud 1972. See Figure 5.

7. Root-end filling material (seven trials, 846 participants)

Seven studies each compared two different materials for root-end filling.

MTA (mineral trioxide aggregate) ***versus IRM*** (intermediate restorative material) was evaluated by two studies that involved 222 participants (Chong 2003; Lindeboom 2005b). After one-year follow-up, there was no evidence of a difference between groups in clinical and radiographic success, as shown in Analysis 7.1 (RR 1.09, 95% CI 0.97 to 1.21). There was no heterogeneity between the two studies' results (P value = 0.72). Only one study provided healing outcomes at two-year follow-up (Chong 2003), showing no evidence of a difference between groups, as shown in Analysis 7.2 (RR 1.05, 95% CI 0.92 to 1.20; P = 0.45).

Only one study evaluated postoperative pain (Chong 2003). The comparison up to two days post surgery was based on the proportion of participants experiencing postoperative pain and found no evidence of a difference at one day (RR 0.99, 95% CI 0.82 to 1.19; P = 0.88) or at two days (RR 1.06, 95% CI 0.83 to 1.36; P = 0.62) (Analysis 7.3).

MTA versus SuperEBA was evaluated by one study that involved 192 participants (Song 2012). After one-year follow-up, there was no evidence of a difference in clinical and radiographic success, as shown in Analysis 7.4 (RR 0.97, 95% CI 0.91 to 1.04).

MTA versus gutta-percha smoothing was evaluated by one study at high risk of bias that involved 44 participants (Christiansen 2009). . There was evidence of better healing when the root-end was filled with MTA as compared with treatment of the root-end by smoothing of the orthograde GP root filling, after one-year follow-up, as shown in Analysis 7.5 (RR 1.60, 95% CI 1.14 to 2.24).

The study assessed postoperative pain using a VAS scale and showed no evidence of a difference in pain evaluated at one day (MD -4.00, 95% CI -16.69 to 8.69; P = 0.54), 2 days (MD 2.00, 95% CI -6.22 to 10.22; P = 0.63) and three days post surgery (MD 5.00, 95% CI -4.37 to 14.37; P = 0.30), as shown in Analysis 7.6.

Glass ionomer cement versus amalgam was evaluated in one study a high risk of bias that involved 85 participants/105 teeth (Zetterqvist 1991); the analysis was tooth-based. After one-year follow-up, there was no evidence of a difference in clinical and radiographic success (P = 0.78), as shown in Analysis 7.7 (RR 0.98, 95% CI 0.86 to 1.12). After five years of follow-up, some participants dropped out and the population was reduced to 64 participants/67 teeth. Results showed no evidence of a difference in clinical and radiographic success at the five-year follow-up (P = 1.00), as shown in Analysis 7.8 (RR 1.00, 95% CI 0.84 to 1.20).

IRM versus gutta-percha was evaluated by one study at high risk of bias that involved 139 participants/160 teeth (Walivaara 2009); 147 teeth in 131 participants were evaluated at the one-year follow-up. Fractured teeth at one-year follow-up (three in the IRM group and one in the gutta-percha group) were considered as failures instead of being excluded as in the Walivaara 2011 study. After one-year follow-up, results showed no evidence of a difference in clinical and radiographic success (P = 0.22) between the two groups, as shown in Analysis 7.9 (RR 0.92, 95% CI 0.80 to 1.05).

IRM versus SuperEBA was evaluated by one study at high risk of bias that involved 164 participants/206 teeth (Walivaara 2011); 194 teeth in 153 participants were assessed at the one-year follow-up. After one-year follow-up, in spite of a tendency in favour of

IRM group, there was no clear evidence of a difference in clinical and radiographic success, as shown in Analysis 7.10 (RR 1.11, 95% CI 0.99 to 1.24; P = 0.07).

8. Grafting versus no grafting (four trials, 106 participants)

One study at unclear risk of bias that involved 18 participants/18 teeth evaluated calcium sulphate versus no grafting (Pecora 2001). After one-year follow-up, there was no evidence of better healing when calcium sulphate was used (P = 0.46), as shown in Analysis 8.1 (RR 1.12, 95% CI 0.83 to 1.50).

One study at high risk of bias (Taschieri 2007), which involved 41 participants/59 teeth, assessed guided tissue regeneration (GTR) using bovine bone mineral and resorbable collagen membrane versus no GTR. The analysis was tooth-based. After one-year follow-up, results showed no evidence of better healing when GTR was used (P = 0.39), as shown in Analysis 8.2 (RR 1.12, 95% CI 0.86 to 1.46).

Plasma rich in growth factors (PRGF) versus no grafting was evaluated in one study at high risk of bias (Del Fabbro 2012), which assessed postoperative pain and symptoms up to one week in 36 participants. There was evidence of less pain among participants treated with the adjunct of PRGF, as shown in Analysis 8.3 (one day: MD -51.60, 95% CI -63.43 to -39.77; P < 0.001; two days: MD -41.70, 95% CI -52.09 to -31.31; P < 0.001; three days: MD -45.00, 95% CI -59.7 to -30.29; P < 0.001).

Platelet-rich fibrin versus no grafting was evaluated in one study at high risk of bias (Angerame 2015), which assessed radiographic healing up to one year after surgery, pain and swelling up to seven days postoperatively, and the occurrence of complications such as sinus tract apicomarginal communication and infection with tenderness to palpation or percussion. This study claimed to be preliminary and had a small sample size (only seven participants in the test group and four in the control group), which prevented a robust analysis. Study authors reported that after one-year follow-up, they found no significant difference in healing of the lesion between test and control groups, and they were able to observe a significant difference only at two-month and three-month follow-up. The article included no report of complications, and the study authors replied that none occurred throughout the observation period. Pain was not assessed by means of a VAS scale, so we could not compare these findings with those of other studies. Pain was reported to be significantly less among participants treated with PRF adjunct at two time points only, two and six hours after surgery. Swelling was reported to be significantly less in the PRF group up to five days postoperatively.

9. Low energy level laser therapy (LLLT) versus placebo versus control (one study, 72 participants)

One study at high risk of bias evaluated the effects of LLLT irradiation performed intraoperatively at one, three and seven days after surgery (Payer 2005). There was no evidence of a difference between participants treated with LLLT and those in the placebo group (irradiation without laser activation) or control group (no use of the laser device) in terms of swelling, wound healing and pain, as evaluated at one, three and seven days post surgery. Pain evaluated by VAS (0 to 100 scale) and a numerical rating scale (NRS; 1 to 10 scale) was reported only in graphic form, and study authors were not able to provide actual means and standard deviations to allow a quantitative evaluation. Pain evaluated by a verbal rating scale (VRS; scored as no pain or slight, moderate, strong and very strong pain) represented the maximum pain levels experienced by participants in the first postoperative week. In all cases, maximum pain occurred on the first day after surgery (Payer 2005). For this analysis, we aggregated data from "moderate" + "minor" scores (low pain) and from "strong" and "very strong" scores (high pain) and considered the latter as events in Analysis 9.1 (LLLT versus control: RR 0.04, 95% CI 0.00 to 0.71; placebo versus control: RR 0.04, 95% CI 0.00 to 0.61).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

CBCT versus periapical radiography					
Patient or population: people requiring retreatment of periapical lesions **Setting:** university **Interventions:** CBCT vs periapical radiography					
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)** Comments
	Risk with periapical radiography	**Risk with CBCT**			
Healing - 1 year	737 per 1000	752 per 1000 (516 to 1000)	RR 1.02 (0.70 to 1.47)	39 (1 RCT)	⊕◯◯◯ **very low**[a]
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed				
Prevalence of pain - 1 day	Not assessed				
Occurrence of postoperative infection - 4 weeks	Not assessed				
Height loss of interdental papilla	Not assessed				
Maximum pain assessed with verbal rating scale (VRS)	Not assessed				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Quality of evidence was downgraded because it was derived from a single study at high risk of bias with imprecise results.

Preoperative antibiotic prophylaxis versus placebo

Patient or population: people requiring retreatment of periapical lesions
Setting: university
Interventions: preoperative antibiotic prophylaxis vs placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with antibiotic prophylaxis				
Healing - 1 year	Not assessed					
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	32 per 1000	16 per 1000 (3 to 85)	RR 0.49 (0.09 to 2.64)	250 (1 RCT)	⊕◯◯◯ **very low**[a]	
Height loss of interdental papilla	Not assessed					
Maximum pain assessed with verbal rating scale (VRS)	Not assessed					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Quality of evidence was downgraded because it was derived from a single study at unclear risk of bias with very imprecise results.

Different types of magnification devices

Patient or population: people requiring retreatment of periapical lesions
Setting: university
Interventions: magnification devices

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with loupes or microscope	Risk with endoscope				
Loupes vs endoscope - healing at 1 year	906 per 1000	952 per 1000 (834 to 1000)	RR 1.05 (0.92 to 1.20)	62 (71 teeth) (1 RCT)	⊕⊕◯◯ **low**[a]	
Microscope vs endoscope - healing at 2 years	902 per 1000	911 per 1000 (803 to 1000)	RR 1.01 (0.89 to 1.15)	70 (100 teeth) (1 RCT)	⊕⊕◯◯ **low**[a]	
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla	Not assessed					

Maximum pain assessed with verbal rating scale (VRS)	Not assessed

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Quality of evidence was downgraded because it was derived from a single study at high risk of bias.

Papilla base incision (PBI) versus complete mobilisation

Patient or population: people requiring retreatment of periapical lesions
Setting: university
Intervention: PBI vs complete mobilisation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with complete mobilisation	Risk with PBI				
Healing - 1 year	Not assessed					
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Mean pain was 90 mm	Mean pain in the intervention group was 2.25 lower (7.17 lower to 2.67 higher)	-	38 (1 RCT)	⊕◯◯◯ **very low**[a]	
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla - 1 year	Mean height loss of interdental papilla was 0.98 mm.	Mean height loss of interdental papilla in the intervention group was 1.04 mm lower (1.48 lower to 0.60 lower)	-	12 (1 RCT)	⊕◯◯◯ **very low**[b]	
Maximum pain assessed with verbal rating scale (VRS)	Not assessed					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Quality of evidence was downgraded because it was derived from a single small study at unclear risk of bias with very imprecise results.
[b] Quality of evidence was downgraded because it was derived from one small split-mouth study at high risk of bias.

Ultrasonic instruments versus bur

Patient or population: people requiring retreatment of periapical lesions
Setting: university
Intervention: ultrasonic instruments vs bur

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with bur	Risk with ultrasonic				
Healing - 1 year	709 per 1000	809 per 1000 (709 to 922)	RR 1.14 (1.00 to 1.30)	290 (1 RCT)	⊕⊕◯◯ **low**[a]	There was inconclusive evidence that use of ultrasonic devices could produce a better success rate after 1-year follow-up
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla	Not assessed					
Maximum pain assessed with verbal rating scale (VRS)	Not assessed					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Quality of evidence downgraded because it was derived from one study at high risk of bias (attrition bias).

Different types of root end fillings						
Patient or population: people requiring retreatment of periapical lesions **Settings:** university hospital						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Intermediate restorative material (IRM)	**Mineral trioxide aggregate (MTA)**				
Healing - 1 year	806 per 1000	878 per 1000 (781 to 975)	RR 1.09 (0.97 to 1.21)	222 (2 RCTs)	⊕⊕◯◯ **low**[a,b]	RR after 2 years as computed on 108 participants (1 study) was 1.05 (95% CI 0.92 to 1.20)
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	815 per 1000	823 per 1000 (684 to 994)	RR 1.01 (0.84 to 1.22)	100 (1 RCT)	⊕⊕◯◯ **low**[a,b]	RR after 2 days as computed on 100 participants (1 study) was 0.94 (95% CI 0.73 to 1.20)
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla	Not assessed					

Maximum pain assessed with verbal rating scale (VRS)	Not assessed					
	MTA	**SuperEBA**				
Healing - 1 year	956 per 1000	927 per 1000 (870 to 994)	RR 0.97 (0.91 to 1.04)	192 (1 RCT)	⊕⊕◯◯ **low**[c]	There was no evidence of a difference in success rate after 1-year follow-up when MTA or SuperEBA was used as root-end filler
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla	Not assessed					
Maximum pain assessed with verbal rating scale (VRS)	Not assessed					
	Gutta-percha	**MTA**				

Healing - 1 year	619 per 1000	990 per 1000 (706 to 1000)	RR 1.60 (1.14 to 2.24)	46 (1 RCT)	⊕⊕◯◯ **low**[c]	There was evidence of better healing rate after 1-year follow-up when MTA as compared with gutta-percha was used
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Mean pain in the control group was 21.	Mean pain in the intervention groups was 4 units lower (-16.69 to 8.69).		42 (1 RCT)	⊕⊕◯◯ **low**[c]	After 2 days, mean difference in pain was 2.00 (-6.22 to 10.22); after 3 days, mean difference in pain was 5.00 (-4.37 to 14.37)
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla	Not assessed					
Maximum pain assessed with verbal rating scale (VRS)	Not assessed					
	Amalgam	**Glass ionomer cement**				
Healing - 1 year	904 per 1000	886 per 1000 (777 to 1000)	RR 0.98 (0.86 to 1.12)	105 (1 RCT)	⊕◯◯◯ **very low**[a,d]	RR after 5 years as computed on 82 participants (1 study) was 1.00 (95%CI 0.84 to 1.20)

Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla	Not assessed					
Maximum pain assessed with verbal rating scale (VRS)	Not assessed					
	Gutta-percha	**IRM**				
Healing - 1 year (or longer)	885 per 1000	814 per 1000 (708 to 929)	RR 0.92 (0.80 to 1.05)	147 (1 RCT)	⊕◯◯◯ **very low**[a,d]	There is no evidence of a difference in success rate after 1-year follow-up when gutta-percha or IRM was used as root-end filler
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	Not assessed					

Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla	Not assessed					
Maximum pain assessed with verbal rating scale (VRS)	Not assessed					
	IRM	**SuperEBA**				
Healing - 1 year (or longer)	816 per 1000	906 per 1000 (808 per 1000)	RR 1.11 (0.99 to 1.24)	194 (1 RCT)	⊕○○○ **very low**[a,d]	There was no evidence of a difference in success rate after 1-year follow-up when SuperEBA or IRM was used as root-end filler
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla	Not assessed					

Maximum pain assessed with verbal rating scale (VRS)	Not assessed

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Quality of evidence was downgraded owing to imprecision (CI includes RR of 1.0).
[b] Quality of evidence was downgraded because one study had high risk of bias (attrition bias).
[c] Quality of evidence was downgraded because it was based on a single study and because of imprecision.
[d] Quality of evidence was downgraded because it was based on a single study that had high risk of bias.

Grafting versus no grafting

Patient or population: people requiring retreatment of periapical lesions
Settings: university
Intervention: grafting
Control: no grafting

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No grafting	Grafting				
Healing - 1 year		**Calcium sulphate**				
	889 per 1000	996 per 1000 (738 per 1000)	RR 1.12 (0.83 to 1.50)	18 (1 RCT)	⊕⊕◯◯ **low**[a]	There was no evidence that grafting the periapical lesion with calcium sulphate may improve healing of the lesion after 1-year follow-up
		GTR + Bovine bone				
	743 per 1000	832 per 1000 (639 per 1000)	RR 1.12 (0.86 to 1.46)	59 (1 RCT)	⊕⊕◯◯ **low**[a]	There was no evidence that guided tissue regeneration improves healing of the lesion after 1-year follow-up
		PRGF gel				

Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Mean pain was 73.3.	Mean pain in the intervention group was 51.6 lower (63.43 lower to 39.77 lower)	-	36 (1 RCT)	⊕⊕◯◯ **low**[a]	There was evidence that using plasma rich in growth factors may decrease postoperative pain in the early days after surgery. After 2 days, mean pain in the intervention group was 41.7 lower than in the control group (-52.09 to -31.31); after 3 days, mean pain in the intervention group was 45 lower than in the control group (-59.71 to -30.29)
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla	Not assessed					
Maximum pain assessed with verbal rating scale (VRS)	Not assessed					

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Quality of evidence was downgraded two levels because it was based on a single study and because of imprecision.

Low energy level laser therapy compared with placebo for surgical retreatment of periapical lesions

Patient or population: people requiring retreatment of periapical lesions
Setting: university
Intervention: low energy level laser therapy (LLLT)
Control: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	LLLT				
Healing - 1 year	Not assessed					
Pain assessed with visual analogue scale (VAS) from 0 to 100 - 1 day	Not assessed					
Prevalence of pain - 1 day	Not assessed					
Occurrence of postoperative infection - 4 weeks	Not assessed					
Height loss of interdental papilla - 1 year	Not assessed					
	Placebo	**LLLT**				
Maximum pain assessed with verbal rating scale (VRS)	**0 per 1000**	**0 per 1000**	Not estimable	52 (1) RCT	⊕○○○ **very low**[a]	

	Control	LLLT			
Maximum pain assessed with verbal rating scale (VRS)	**300 per 1000**	**0 per 1000**	Not estimable	44 (1) RCT	⊕◯◯◯ **very low**[a]

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Quality of evidence was downgraded three levels because it is based on a single study at high risk of bias.

DISCUSSION

Summary of main results

We performed this review to update a previous Cochrane review, published in 2007 (Del Fabbro 2007), which addressed the comparison between surgical and root canal retreatment for periapical lesions. The present version expanded the initial aim to include an evaluation of different aspects of surgical root canal treatment.
We identified two studies that compared a surgical and a non-surgical approach, both of which were included in the previous version of this review. Thomas Kvist, the author of the study with four-year follow-up (Kvist 1999), kindly provided us with results of treatment after 10 years of follow-up. These results indicate the absence of a difference between the two groups.
We identified 18 studies comparing different surgical approaches. One study evaluated the importance of modern radiographic diagnostic tools in the preoperative phase, finding no significant advantage of using preoperative CBCT instead of periapical radiographs in terms of healing of the lesion after one-year follow-up (Kurt 2014).
One study evaluated the value of antibiotic prophylaxis for reducing postoperative infection in a cohort of 256 participants up to four weeks post surgery, but found no evidence of a difference between groups for the incidence of infective episodes (Lindeboom 2005a).
Two studies addressed the hypothesis that a minimally invasive incision like the papilla base incision (PBI) could have beneficial results in root-end resection as compared with a traditional flap (complete papilla mobilisation). One parallel-design study found that the PBI led to reduced postoperative pain and discomfort (Del Fabbro 2009). The other study, which used a split-mouth design (Velvart 2004), found inconclusive evidence that PBI produced a better aesthetic outcome in terms of interdental papilla height after one year of healing. Both of these trials had a limited sample size, and their suggested benefits need to be confirmed by further evidence.
The benefit of magnification devices was explored in a three-arm trial that, unfortunately, did not include a control group without magnification (Taschieri 2008). Therefore, the true efficacy of a given magnification device could not be evaluated. The only conclusion of this tooth-based study was that there is no evidence of a difference in healing of the lesion after one year or after two years, using microscope, endoscope or loupes during the surgical procedure. Technical and practical advantages of magnification devices in enhancing the view of the surgical field and consequently improving precision and surgeon comfort during the operation have been claimed often but never quantified.
One trial evaluated use of an ultrasonic device versus a conventional handpiece bur for root-end preparation (De Lange 2007). The analysis showed inconclusive evidence of an advantage of the ultrasonic device, supporting the benefits claimed for this technology for bone surgery and many surgical applications in the oral field.
Seven of the included trials compared different retro-filling materials, evaluating healing after one year (Christiansen 2009; Lindeboom 2005b; Song 2012; Walivaara 2009; Walivaara 2011) or longer (Chong 2003; Zetterqvist 1991). Two of these studies also assessed postoperative pain and symptoms (Chong 2003; Christiansen 2009). Only one comparison showed evidence of a difference between groups in terms of periapical healing at one year, with the group having root-end filled with mineral trioxide aggregate (MTA) displaying better results than the group treated with gutta-percha (Christiansen 2009). The other six studies showed no evidence of differences in outcomes between materials tested, suggesting that the effect of root-end filling material per se might be considered of minor importance to the success of retreatment. It should be noted that the type of material used in filling the retrograde cavity did not represent the only difference in the protocols adopted for root-end resection in these seven studies. For example, in Zetterqvist 1991, investigators used a traditional technique, without magnification devices and with an inverted cone bur in preparing the retrograde cavity. The other studies adopted a modern technique, with microsurgical ultrasonic instruments for retrograde cavity preparation; investigators used a surgical microscope (Chong 2003; Christiansen 2009; Song 2012) or loupes (Lindeboom 2005b; Walivaara 2009; Walivaara 2011) to enhance root-end visualisation.
Another question in endodontic surgery is whether filling the periapical lesion with a graft material improves healing of the lesion. Four studies addressed this question, but their protocols were too different to allow meta-analysis. Pecora 2001 found no evidence of benefit derived from grafting the lesion with calcium sulphate when evaluating healing of the lesion after one-year follow-up. Taschieri 2007 failed to demonstrate evidence of an advantage of guided tissue regeneration (GTR) for the treatment of large periapical lesions of strict endodontic origin. Del Fabbro 2012 found evidence of a benefit of plasma rich in growth factors in reducing postoperative pain during the first three days after surgery. Unfortunately, no data are currently available regarding healing of the lesion at one-year follow-up, thereby preventing any comparison with other studies evaluating the effects of grafting the lesion. Angerame 2015 reported a significant benefit of platelet-rich fibrin in reducing both postoperative pain and swelling. The study reported significantly better healing of the lesion two and three months after surgery but not at 12-month follow-up. This preliminary study had a very small sample size, so results should be interpreted cautiously.
One study addressed the efficacy of low energy level laser therapy (LLLT) for reducing postoperative pain and swelling in root-end resection, showing no evidence of differences in outcomes between LLLT and placebo (irradiation without laser activation), although both caused less pain as compared with the control (without use of the laser device) (Payer 2005). This suggests that LLLT is ineffec-

tive in preventing postoperative pain and confirms the importance of the placebo group for outcomes based on subjective evaluation.

Overall completeness and applicability of evidence

Most studies were performed in university clinics or in non-academic specialised clinical centres, by experienced operators. Therefore, generalisation of results from the present review to different clinical settings, such as general daily practice, should be made with caution. Studies comparing the same interventions were insufficient to enable robust conclusions to be drawn via meta-analysis. We found several indications of possible advantages of some procedures or materials over others, but no definitive evidence for almost any of the topics addressed.

In most cases, outcomes were restricted to the one-year follow-up period. Although this does allow comparison of results from different studies after the same observation period, it does not consider the fact that in surgical procedures, risk of emerging post-treatment disease might increase over time. This fact was underlined only by Kvist 1999, which reported relapses in four surgically treated participants at between one and four years of follow-up, but no recurrence for participants who underwent root canal retreatment. Thus, outcomes at one year may not actually reflect the longer-term outcomes of which both clinicians and patients need to be aware.

Quality of the evidence

Most of the studies included in this review provided data on assessment of the primary outcome of this review, that is, they investigated the efficacy of different endodontic surgical protocols by performing clinical and radiographic evaluations of healing of periapical pathosis after at least one year of follow-up. Other outcomes addressed were the effects of different surgical protocols on postoperative pain and symptoms. The quality of the available evidence quality is low to very low. The risk of bias in most of the included studies was unclear, with most possible sources of bias due to lack of allocation concealment and blinding of operators, participants and evaluators, especially in Walivaara 2009, Walivaara 2011 and Zetterqvist 1991, which also omitted most information regarding the source of funding, the characteristics of participants, the teeth and the lesions. Zetterqvist 1991 had a dropout rate higher than 20% at five-year follow-up, thereby reducing the statistical power of the analysis and the robustness of the outcomes provided. Furthermore, in these three studies, some participants had more than one tooth treated and data were provided with only the tooth - not the participant - considered as the analysis unit. Finally, in the two studies by Walivaara (Walivaara 2009; Walivaara 2011), investigators reported no specific follow-up time, but they followed teeth for at least 12 months, in a range between 12 and 38 months (Walivaara 2009) and 12 to 21 months (Walivaara 2011). This raises some concerns about the way these trials were conducted and the reliability of results reported by these investigators.

The size of the lesion, which is an important parameter often correlated with the likelihood of healing, was not the same across all included studies, ranging from smaller than 5 mm (small lesions) to larger than 10 mm (large lesions), and nine out of 20 included studies did not even report the lesion size (Angerame 2015; Chong 2003; Christiansen 2009; De Lange 2007; Kurt 2014; Song 2012; Velvart 2004; Walivaara 2009; Zetterqvist 1991). This could be a concern when the trials are compared.

Sample size was variable among studies, ranging from 11 participants (Angerame 2015) to 260 participants (Song 2012). Only eight out of 19 studies reported a sample size calculation, and in most cases, the sample size appeared underpowered to detect a significant difference.

Potential biases in the review process

This review did not consider studies performed with the traditional root-end resection technique (e.g. Kvist 1999; Zetterqvist 1991) separately from studies performed using a modern root-end resection technique, which represent the majority of included trials. This means that potentially important differences in the protocols might not be fully accounted for. Indeed, several studies sought to compare specific aspects of the traditional technique versus the modern one, but in general, standardisation among these studies was poor, which might hinder any comparison and limit the precision of the success estimate.

Some authors of the present review (MDF, ST) are also among the authors of some of the included studies (Del Fabbro 2009; Del Fabbro 2012; Taschieri 2007; Taschieri 2008). We addressed this bias by excluding these authors from any evaluation concerning the studies in which they were involved.

Furthermore, some of the parameters accounted for are patient-based outcomes, such as pain, aesthetics and satisfaction, which are subjective. The individual judgement of patients may depend on factors such as their expectations and their previous experience. However, as we found no clear evidence suggesting that apical periodontitis is a life-threatening disease, such patient-based outcomes may represent a sensible contribution to assessment of treatment success.

Agreements and disagreements with other studies or reviews

Other systematic reviews and meta-analyses have addressed some aspects of root-end resection, such as outcomes of modern techniques (Tsesis 2009; Tsesis 2013), comparison of traditional root-end surgery and root-end microsurgery (Setzer 2010), effects of

using guided tissue regeneration (Tsesis 2011), use of regenerative techniques (Von Arx 2011), comparison of root-end microsurgery with and without the use of higher magnification (Setzer 2012) and factors affecting prognosis (Von Arx 2010b). However, because the findings of these reviews were not based on the most reliable clinical studies owing to less restrictive inclusion criteria with respect to the present review, direct comparison with the present findings could be inappropriate and difficult to interpret.

AUTHORS' CONCLUSIONS

Implications for practice

The review found that neither root-end resection nor root canal retreatment was superior for healing at one year; however, root canal retreatment produced less postoperative pain and swelling than root-end resection with root-end filling.

The surgical approach to retreatment of periapical lesions through root-end resection with or without root-end filling has changed considerably since its inception because of the introduction of various materials, devices and techniques that aim to improve success rates of treatment, reduce recurrence of disease and lessen patient discomfort in the postsurgical phase. Although the studies included in this review addressed many different aspects of the surgical procedure, unfortunately, the overall evidence emerging from the included trials is limited and incomplete; for most of the comparisons considered, only one study provided data.

The only surgical technique that significantly increased clinical and radiographic healing of the periapical lesion after at least one year of follow-up was the use of ultrasonic devices instead of the conventional handpiece bur for root-end preparation.

This review also found that antibiotic prophylaxis does not seem to reduce the incidence of postoperative infection; use of platelet concentrates as an adjunct to the surgical procedure may markedly reduce postoperative pain; and use of a papilla base incision may help to preserve the interdental papilla.

Overall, none of the review findings can be assumed to be conclusive, as the quality of the evidence was low to very low. Information is still insufficient to inform clinicians whether root canal retreatment or root-end resection should be used, and which procedures for root-end resection should be followed to achieve the best results for patients.

Implications for research

The review authors are aware of the difficulties of carrying out large-scale, long-term randomised studies, especially regarding the financial resources needed to perform appropriate well-designed studies; however, without consistent results from such studies, no reliable answers to pending questions can be found. All questions addressed in this review need further investigation if we are to understand whether a surgical or a non-surgical approach should be used, and which surgical procedures may provide the best and most predictable results, in terms of healing of periapical lesions and quality of life of the patient in the postoperative period. Future studies should use standardised techniques and success criteria, precisely defined outcomes and specific features of the periapical lesion. Investigators should use the participant - not the tooth - as the analysis unit, if possible, and should follow the CONSORT recommendations for reporting (www.consort-statement.org).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Angerame 2015

Methods	Trial design: randomised, parallel-group trial Location: Trieste, Italy Study centres: Dental Clinic, University Clinical Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy Recruitment period: not stated Source of funding: none Ethical approval: not stated Number of surgeons: 1
Participants	Inclusion criteria: adults presenting a tooth with persisting periapical radiolucency, the presence of fistula and symptoms after orthograde root canal retreatment and a high risk of jeopardising the root integrity by the orthograde approach Exclusion criteria: severe systemic disorders (i.e. non-controlled diabetes, immunological disease, malignant neoplastic process), thrombocytopenia, insufficient compliance Age at baseline: 46.8 ± 11.6 years (range 28 to 72 years) Gender: W6/M5 Smokers: not specified Teeth treated: various types Number randomised (participants/teeth): 11/11 Number evaluated (participants/teeth): 11/11 at 12 months Size of lesion: unspecified
Interventions	Comparison: apical surgery by leaving the cavity empty vs filling with platelet-rich fibrin (PRF) Test group: apical surgery plus PRF (participants/teeth): 7/7 Control group: only apical surgery (participants/teeth): 4/4 Surgical technique: root-end resection; in both groups, the microscope was used for root-end management; root-end preparation was made by ultrasonic instruments; SuperEba cement was used as root-end filler Follow-up duration: 12 months
Outcomes	Periapical healing assessed by clinical and radiographic evaluation according to the criteria of Molven 1987 at 1, 2, 3, 4, 5, 6, 12 months: • Presence of postoperative complications at each follow-up visit • Pain and swelling evaluated on a 0 to 3 scale by a questionnaire filled out by participants at 2, 6 and 12 hours and each day during the first postoperative week
Notes	Sample size calculation was not performed; radiographs were blindly examined twice at interval ≥ 30 days; no detail on lesion size was provided

Risk of bias

Bias	Authors' judgement	Support for judgement

Angerame 2015 (*Continued*)

Random sequence generation (selection bias)	Low risk	Simple computerised randomisation procedure was performed.
Allocation concealment (selection bias)	High risk	This was not done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was impossible to blind the operator using PRF and participants from whom blood was drawn for PRF preparation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The 2 evaluators of radiographs were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the final analysis
Selective reporting (reporting bias)	Unclear risk	All outcomes were adequately reported, except for complications. Study authors replied that no complications occurred
Other bias	High risk	No details on recruitment period, smoking or lesion size were provided. It is unclear how sample size was decided

Chong 2003

Methods	Trial design: randomised, parallel-group trial Location: London, UK Study centres: Dept. of Conservative Dentistry, GKT Dental Institute, King's College London, Guy's Hospital London, UK Recruitment period: not stated Source of funding: DHSC London, Research & Development, Responsive Funding Programme Ethical approval: yes (local ethical committee) Number of surgeons: 2
Participants	Inclusion criteria: adult patients with periapical lesions diagnosed radiographically. The involved teeth had adequate root canal filling and crown. Periodontal probing depth < 4 mm, except for unilocular sinus tract Exclusion criteria: failure to satisfy entry criteria Age at baseline: not specified Gender: not specified Smokers: not specified Teeth treated: single-rooted anterior teeth, 1 root of premolar teeth, mesio-buccal root of maxillary molars Number randomised (participants/teeth): 183/183 Number evaluated (participants/teeth): 122/122 at 12 months, 108/108 at 24 months;

Chong 2003 (*Continued*)

	in Chong 2005: n = 100 participants (54 questionnaires in IRM group and 46 in MTA group were deemed correctly completed) Size of lesion: unspecified
Interventions	Comparison: mineral trioxide aggregate (MTA) vs intermediate restorative material (IRM) as root-end filler in root-end resection Test group: MTA (Loma Linda University, Loma Linda, CA, USA) (n = 64 participants/64 teeth after 12 months and n = 61 participants/61 teeth after 24 months) Control group: IRM (Dentsply, Konstanz, Germany) (n = 58 participants/58 teeth after 12 months and n = 47 participants/47 teeth after 24 months) Surgical technique: root-end resection with ultrasonic instrument used for root-end preparation Operating microscope was used to check root-end filling adaptation Follow-up duration: 24 months (48 hours in Chong 2005)
Outcomes	Periapical healing assessed by clinical and radiographic evaluation according to the criteria of Molven 1987 Postoperative pain assessed by VAS and counts of analgesics at 3 to 5 hours, 24 hours and 48 hours after surgery (in Chong 2005)
Notes	Sample size calculation was performed. Radiographs were reassessed after 2 to 3 months to ensure reproducibility. Intraobserver and interobserver agreement was assessed by Cohen's kappa statistics Questionnaires not evaluated were not returned or were excluded if the writing was illegible or the information entered was incomplete (Chong 2005). Scarce details were provided about participant demographics, defect characteristics and tooth type distribution in the 2 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation process was carried out on the day of surgery.
Allocation concealment (selection bias)	Low risk	One of the research team members picked a sealed envelope from a pack to learn which material should be used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was not specified.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Postoperative radiographs were assessed by independent trained observers
Incomplete outcome data (attrition bias) All outcomes	High risk	34% of participants failed to return, and no reasons were given for dropouts ("patients failed to attend"). However, it is stated, "All

Chong 2003 (*Continued*)

		reasonable methods were used to encourage and pursue all review patients including the offer to reimburse their travel costs." Only 100 questionnaires were evaluated.
Selective reporting (reporting bias)	Low risk	All outcomes were adequately reported.
Other bias	Unclear risk	No details on recruitment period, participant age, gender, smoking or lesion size were provided

Christiansen 2009

Methods	Trial design: randomised, parallel-group trial (18 participants per group); 8 more patients had 2 teeth treated (split-mouth); another article (Christiansen 2008) reported on a subgroup of participants in the same trial Location: Aarhus, Denmark Study centres: 1; University of Aarhus, Denmark Recruitment period: June 2005 to October 2006 Source of funding: "research stipend from the Faculty of Health Sciences, University of Aarhus, Denmark" (Christiansen 2008); the Danish Dental Association (Calcinfonden) was acknowledged for support (Grant No. FORSKU 2005) Ethical approval: yes (regional Committee of Ethics; N.reg. clinicaltrials.gov: ID: NCT00228280) Number of surgeons: 1
Participants	Inclusion criteria: incisor, canine or premolar with sufficient orthograde root filling regarding length and density, and with a periapical lesion, which was unchanged in size or had progressed during at least a 2-year period. Marginal bone level around the tooth in question should be reduced by no more than 50%. Exclusion criteria: presence of visible gaps between root filling and dentin wall; severe periodontitis Age at baseline: 54.6 ± 11.9 years (range 30 to 77 years); in Christiansen 2008, average 54.4 years (range 30 to 68 years) Gender: W24/M20; in Christiansen 2008, W23/M19 Smokers: 16/44; in Christiansen 2008, 6/18 control group; 7/24 test group Teeth treated: 17 incisors/24 maxillary canines and premolars, 11 mandibular canines and premolars Number randomised (participants/teeth): 44/52 (8 participants contributed with 2 teeth each: 1 tooth per group); in Christiansen 2008, 42/42 Number evaluated (participants/teeth): 39/46; in Christiansen 2008, 42/42 Size of lesion: not specified (PAI score evaluated)
Interventions	Comparison: MTA vs smoothening of orthograde gutta-percha root filling Test group: MTA as root-end filler (mineral trioxide aggregate, n = 26 participants/26 teeth) Control group: smoothening of orthograde gutta-percha (n = 26 participants/26 teeth) Surgical technique: root-end resection; in MTA group, root-end cavity was prepared

	with the use of diamond-coated Surgical Endo Tips mounted in an ultrasonic scaler. The root-end surface was visualised under a surgical microscope Follow-up duration: 12 months
Outcomes	Periapical healing assessed by clinical and radiographic evaluation (Molven 1987, Rud 1972) by blinded observers; in Christiansen 2008, a visual analogue scale (VAS) and a questionnaire used to assess postoperative pain, swelling and discomfort the first 3 days after surgery
Notes	Sample size calculation was not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed at participant level, by drawing lots at the time of treatment delivery. Eight participants had 2 teeth; the first was randomised and the second underwent the opposite treatment, in the same surgical session
Allocation concealment (selection bias)	Unclear risk	This was not done because treatment was allocated at the time of delivery
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not stated.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Each radiograph...was blinded to treatment method by masking apical root filling."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data were provided for all participants evaluated. All dropouts (5 participants/6 teeth) were accounted for, and reasons were explained
Selective reporting (reporting bias)	Low risk	All outcomes were adequately reported.
Other bias	Low risk	None was detected.

Danin 1996

Methods	Trial design: randomised, parallel-group trial Location: Stockholm, Sweden Study centres: Karolinska Institutet, Huddinge University Hospital, Stockholm, Sweden Recruitment period: not stated Source of funding: grants from the Swedish Dental Association and Praktikertjä nst AB Ethical approval: not stated Number of operators: 1 surgeon for test group (apicoectomy), 1 experienced endodontist for control group (endodontic retreatment) 1-Year follow-up parallel-group randomised trial with 38 participants. 1 participant initially assigned to root canal retreatment group was later excluded because of uncertainty as to whether the periradicular lesion was associated with the tooth in question
Participants	Inclusion criteria: periradicular pathoses with root canal filled incisors, canines and premolars, referred for specialist treatment at the Department of Endodontics, Karolinska Institutet, Stockholm, Sweden. Only 1 tooth per participant and only teeth for which both retreatment and periradicular surgery were technically feasible were included. Exclusion criteria: patients not meeting inclusion criteria Age at baseline: 52 years (range 24 to 80 years) Gender: W17/M20 Smokers: not specified Teeth treated: 28 teeth were single-rooted; 9 were double-rooted Number randomised (participants/teeth): 38/38 Number evaluated (participants/teeth): 37/37 (1 participant in control group was excluded later because of uncertainty as to whether the periradicular lesion was associated with the tooth in question) Size of lesion: ≤ 5 mm: 12 control/13 test; > 5 mm: 6 control/6 test
Interventions	Comparison: root-end resection vs root canal retreatment Test group: root-end resection (n = 19 participants/19 teeth) Control group: root canal retreatment (n = 18 participants/18 teeth) Surgical technique: root-end resection according to the standard, old technique (round bur, apex resected at 45°, no magnificators used, cavity filled with glass ionomer cement) Follow-up duration: 12 months
Outcomes	Clinical and radiographic healing 1 year after retreatment. Radiographs were examined by 2 different calibrated observers. Treatment outcome was assessed according to the criteria of Rud 1972: complete healing, incomplete healing, uncertain healing, unsatisfactory healing (failure). All cases with symptoms were referred to the 'failure' group. In teeth with 2 treated canals, the result of the less successfully treated root was recorded. At 1 year, the success rate for surgical and root canal retreatment was, respectively, 58% (11/19) and 28% (5/18)
Notes	Sample size calculation was not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Danin 1996 (*Continued*)

Random sequence generation (selection bias)	Low risk	Participants were randomly allocated to treatments.
Allocation concealment (selection bias)	High risk	Study authors replied that no allocation concealment was attempted
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was impossible to blind treatments (surgical vs non-surgical)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding to treatment was impossible for radiographic assessment; the 2 calibrated observers were independent
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One participant in the control group was excluded. We believe this did not significantly affect the analysis. All data are presented for all remaining participants
Selective reporting (reporting bias)	Low risk	Healing data were adequately reported.
Other bias	Unclear risk	Sample size calculation was missing; no details on recruitment period, ethics approval or smokers were provided

De Lange 2007

Methods	Trial design: randomised, parallel-group trial Location: Zwolle, Gronngen, The Netherlands Study centres: Isala Klinieken and University Medical Centre in Zwolle, The Netherlands Recruitment period: not stated (duration of recruitment: 14 months) Source of funding: All ultrasonic devices were provided by the Satalec Company, Merignac, France Ethical approval: not stated Number of surgeons: 5 oral and maxillofacial surgeons and 2 residents
Participants	Inclusion criteria: periapical lesion on 1 of the teeth, confirmed on radiograph, previous endodontic treatment more than 6 months earlier Exclusion criteria: root fracture, periodontal origin of apical infection or absence of marginal buccal bone after flap elevation, root perforation, no previous endodontic treatment, previous endodontic surgery Age at baseline: average 42.7 years (range 9 to 79 years) Gender: W173/M117 Smoker: not stated Teeth treated: 58 anterior, 97 premolar, 135 molar Number randomised (participants/teeth): 399/399 Number evaluated (participants/teeth): 290/290 Size of lesion: not stated

De Lange 2007 (*Continued*)

Interventions	Comparison: ultrasonic device vs bur for root-end preparation Test group: ultrasonic device (P-Max Newtron, Satelec, Merignac, France) (n = 149 participants/149 teeth) Control group: round dental bur (Hager & Meisinger GmbH, Neuss, Germany) (n = 141 participants/141 teeth) Surgical technique: endodontic surgery. No magnification devices were used in either group Follow-up duration: 1 year
Outcomes	Clinical and radiographic healing 1 year after retreatment
Notes	Sample size calculation was performed. 24.4% and 30.2% of participants in test and control groups, respectively, were lost to follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Each participant was randomised by a number drawn from a closed box
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was impossible to blind the operator, as he had to use different instruments for root-end preparation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All radiographs were assessed by 2 oral and maxillofacial surgeons blinded to the applied therapy. The randomisation code was broken 1 year after the last participant was included
Incomplete outcome data (attrition bias) All outcomes	High risk	24.4% and 30.2% of randomised participants in test and control groups, respectively, were lost to follow-up Quote: "The relatively large number of patients who were lost to follow-up was categorized as "missing at random" with no relation to the outcome of treatment." All data were reported for all remaining participants evaluated after the scheduled follow-up
Selective reporting (reporting bias)	Low risk	Treatment outcomes were reported adequately. Outcomes were provided according to tooth type and the number of roots treated

De Lange 2007 (*Continued*)

Other bias	High risk	Seven operators performed surgical procedures; the experience and comparability of the seven operators was not specified; it was not mentionet if each operator performed a comparable number of interventions in both treatment groups; no information on smokers and lesion size was provided

Del Fabbro 2009

Methods	Trial design: randomised, parallel-group trial Location: Milano, Italy Study centres: a University clinic (Università degli Studi di Milano, IRCCS Istituto Ortopedico Galeazzi, Milano, Italy) and a private centre (Milano, Italy) Recruitment period: December 2004 to December 2006 Source of funding: none Ethical approval: Institutional Review Board of Milan University Number of surgeons: 1 experienced surgeon
Participants	Inclusion criteria: no general medical contraindications were known for oral surgical procedures (ASA-1 or ASA-2); only 1 tooth required periradicular surgery; tooth treated surgically had a periradicular lesion of strictly endodontic origin (chronic apical periodontitis) not exceeding 10 mm; non-surgical re-treatment was judged not feasible or had previously failed; tooth had an adequate final restoration with no clinical evidence of coronal leakage; apical root canal was devoid of the presence of a post for ≥ 6 mm; no acute symptoms were present Exclusion criteria: presence of any kind of pathosis associated with vertical root fracture; perforation of the furcation area or lateral canal walls; presence of traumatic injury; periodontal bone loss, detected with a periodontal probe (> 4 mm probing depth); bone defects involving buccal and lingual cortical bone; presence of a thin gingival biotype Age at baseline: 36.4 years (range 22 to 59 years) in SI group and 33.7 years (29 to 56 years) in PBI group Gender: W23/M17 Smokers: 15 (6 in SI group, 9 in PBI group) Teeth treated: 40 (31 anterior, 9 premolar) Number randomised (participants/teeth): 40/40 Number evaluated (participants/teeth): 38/38 Size of lesion: < 10 mm
Interventions	Comparison: SI vs PBI Test group: PBI: papilla base incision (participants/teeth): 20/20 Control group: SI: sulcular incision (participants/teeth): 20/20 treated with complete mobilisation of the papilla Surgical technique: root-end resection; in both groups, microscope was used for root-end management; root-end preparation was made by ultrasonic instruments; zinc oxide EBA-reinforced cement was used as root-end filler Follow-up duration: 7 days

Del Fabbro 2009 (*Continued*)

Outcomes	Pain assessment assessed by VAS, quality of life assessed by a questionnaire
Notes	Dropout reasons provided; sample size calculation performed; total time needed for each procedure recorded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomised table was used.
Allocation concealment (selection bias)	Low risk	A closed opaque envelope containing the indication of which surgical flap had to be used was opened before the start of each surgical operation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was impossible to blind the operator performing the incision. Participants were unaware of the type of incision they received
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No evaluator blinding was provided because outcomes were self-assessed by participants, who completed questionnaires. The statistician was blinded to groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the final analysis
Selective reporting (reporting bias)	Low risk	All outcomes were adequately reported.
Other bias	Low risk	None was detected.

Del Fabbro 2012

Methods	Trial design: randomised, parallel-group trial Location: Milano, Italy Study centres: a University clinic (Università degli Studi di Milano, IRCCS Istituto Ortopedico Galeazzi, Milano, Italy) and a private centre (Milano, Italy) Recruitment period: April 2010 to April 2011 Source of funding: none Ethical approval: Institutional Review Board of Milan University Number of surgeons: 1 experienced surgeon
Participants	Inclusion criteria: no general medical contraindications were known for oral surgical procedures (ASA-1 or ASA-2); patients had only 1 maxillary tooth requiring periradicular surgery; tooth had a periradicular lesion of strictly endodontic origin (chronic apical

	periodontitis); minimum diameter of the bone defect, as determined from periapical radiographs, was ≥ 8 mm and ≤ 12 mm; root canal re-treatment was judged unfeasible or had previously failed; tooth had an adequate final restoration without clinical evidence of coronal leakage; apical root canal was devoid of the presence of a post for ≥ 6 mm; no spontaneous pain or swelling was present Exclusion criteria: presence of any kind of pathosis associated with vertical root fracture; presence of through-and-through lesions, diagnosed preoperatively by periapical radiographs, finger palpation and bone probing; perforation of the furcation area or lateral canal walls; known history of traumatic injury; moderate to severe periodontal bone loss, detected with a periodontal probe (probing depth > 5 mm). Patients with neuropsychiatric disorders were also excluded. Age at baseline: 42.4 years (range 34 to 56 years) in test group; 44.8 years (31 to 62 years) in control group Gender: W20/M16 Smokers: 15 (9 in test group, 6 in control group) Teeth treated: 36 (9 lateral incisors, 8 cuspids, 10 premolars, 9 molars) Number randomised (participants/teeth): 18/18 Number evaluated (participants/teeth): 18/18 Size of lesion: 8 to 12 mm
Interventions	Comparison: PRGF adjunct vs modern microsurgery alone Test group: plasma rich in growth factors (PRGF) used to fill the defect and applied on the root-end surface and over the suture (n = 18 participants/18 teeth treated) Control group: no PRGF used (n = 18 participants/18 teeth treated) Surgical technique: root-end resection; in both groups, microscope was used for hard and soft tissue management, and an endoscope was used for root-end management; root-end preparation was performed with ultrasonic instruments; MTA was used as root-end filler Follow-up duration: 7 days
Outcomes	Pain assessed by VAS, quality of life assessed by a questionnaire
Notes	Sample size calculation was performed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The decision to use PRGF was made by a computer-generated randomised table for each participant
Allocation concealment (selection bias)	Low risk	A closed opaque envelope containing the indication of group allocation was opened before the start of each surgical operation
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was impossible to blind the operator using PRGF and participants from whom blood was drawn for PRGF preparation

Del Fabbro 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	No operator blinding was needed because the data (filled questionnaires) were provided by participants. The statistician was blinded to groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the final analysis
Selective reporting (reporting bias)	Low risk	All outcomes were adequately reported.
Other bias	Low risk	None was detected.

Kurt 2014

Methods	Trial design: randomised, parallel-group trial Location: Adana, Turkey Study centres: Department of Oral and Maxillofacial Surgery, Cukurova University Faculty of Dentistry, Adana, Turkey Recruitment period: not stated Source of funding: not stated Ethical approval: yes: The ethical committee of Cukurova University approved the present study (ethical committee report no. 21.05.2009:5:13) Number of surgeons: 1
Participants	Inclusion criteria: patients referred for periradicular surgery of an upper first molar tooth because of an unhealed periradicular lesion despite conventional root canal treatment, a retained root canal instrument fragment, overflow of root canal filling material, or any other idiopathic reason; American Society of Anesthesiologists (ASA) class 1 or ASA class 2; older than 18 years; periodontally healthy adjacent teeth Exclusion criteria: significant systemic medical status (ASA class 3 or higher), acute sinusitis, pregnancy or risk of pregnancy, large lesions that affected the neighbouring teeth, presence of periodontal pathological features, radiolucency at the bifurcation region, smoking habit, a history of radiotherapy at the maxillofacial region, osteoporosis requiring medical therapy, metastatic cancer, alcoholism or drug abuse, physical or mental disability that prevented co-operation Age at baseline: not stated Gender: W18/M22 Smokers: excluded from the study Teeth treated: maxillary first molars Number randomised (participants/teeth): 40/40 Number evaluated (participants/teeth): 39/39 (1 participant from control group was excluded for extensive lesion involvement detected during the procedure. In another participant, the tooth had to be extracted at 6 months because of recurrent infection; the latter was considered a failure concerning treatment outcome, but some parameters could not be assessed at 12 months) Size of lesion: assessed by periodontal probe and CBCT PAI

Kurt 2014 (*Continued*)

Interventions	Comparison: preoperative evaluation with cone beam computed tomography (CBCT) vs conventional (panoramic and periapical) radiography Test group: CBCT (n = 19 participants/19 teeth) Control group: conventional radiography (n = 21 participants/21 teeth) Surgical technique: root-end resection was performed with surgical loupe (3.5× magnification); root-end preparation was done with ultrasonic instruments; root-end cavity was filled with MTA Follow-up duration: 12 months
Outcomes	Clinical and radiographic healing according to Zetterqvist 1991 and Jesslen 1995 criteria; pain, tenderness on apical palpation of buccal and palatal aspects of the tooth; tenderness on horizontal and vertical percussion (all measured on VAS). The presence of swelling, sinus tracts, fluctuation, erythema or abscess was noted, and mobility index and periodontal index of the tooth, as well as perioperative time, were measured
Notes	No sample size calculation was reported; sinus membrane elevation was performed in 92.3% of all participants. Sinus membrane perforation occurred in 20% of participants in group 1 and in 36.8% of participants in group 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A block randomisation technique was used.
Allocation concealment (selection bias)	Unclear risk	This was not specified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Operators were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All radiographs were evaluated by the same person (no double assessment)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rate was low. 1 participant was excluded from the control group for a lesion detected during treatment. In another participant in the test group, the treated tooth had to be extracted owing to infection. All outcomes were reported for remaining participants
Selective reporting (reporting bias)	Unclear risk	Data were reported adequately and in detail for most outcomes, except for VAS scores, which were not presented Quote: "The VAS scores of pain, tender-

Kurt 2014 (*Continued*)

		ness on palpation, and tenderness on percussion in any of the vertical or horizontal directions showed no statistically significant difference between the 2 groups at any of the follow-up sessions (P > .05)." So it was not possible to consider these data for meta-analysis
Other bias	High risk	Sample size calculation was missing; no details on recruitment dates, source of funding or participants' age at baseline were provided; demographic information was limited. It is unclear if and how sinus membrane elevation and sinus membrane perforations reported could have affected outcomes. No specific analysis was done to investigate a possible relationship

Kvist 1999

Methods	Trial design: randomised, parallel-group trial Location: Göteborg, Sweden Study centres: Clinics of Endodontics, Faculty of Odontology, Göteborg University, Sweden Recruitment period: 1989 to 1992 Source of funding: none (information provided by study author) Ethical approval: yes: committee for research on human participants at Göteborg University, Göteborg, Sweden (information provided by study author) Number of surgeons: 1
Participants	Inclusion criteria: Patients with periapical disease ("endodontically failed cases") who were in need of endodontic retreatment; an apical radiolucency was clearly visible; root canal treatment was performed more than 4 years ago, or patient presented with clinical symptoms; no apical-marginal communication was observed; randomisation of retreatment options was considered medically and economically feasible; patient consent was obtained. Exclusion criteria: not meeting inclusion criteria Age at baseline: mean 52 years; test: 53 years (range 28 to 75 years), control: 52 years (17 to 74 years) Gender: test: W29/M16, control: W25/M22 Smokers: not stated Teeth treated: maxillary and mandibular incisors and canines Number randomised (participants/teeth): 92/95 Number evaluated (participants/teeth): 87/90 (at 4-year examination, 3 patients were deceased and 2 withdrawn from the study); in Kvist 2000: 92/95 at 1 week post retreatment Size of lesion: ≤ 5 mm (n = 54) /> 5 mm (n = 41)

Kvist 1999 (*Continued*)

Interventions	Comparison: root-end resection vs root canal retreatment Test group: root-end resection (n = 45 participants/47 teeth) Control group: root canal retreatment (n = 47 participants/48 teeth); 2 weeks elapsed between first phase (preparation of the root canal) and the second phase (root canal filling with resin chloroform and softened gutta-percha)) Surgical technique: standard root-end resection Follow-up duration: 4 years (1 week in Kvist 2000). Study author provided unpublished data on treatment healing at longer follow-up (10 years)
Outcomes	Patients were clinically and radiographically examined 6, 12, 24 and 48 months after retreatment. Radiographs were evaluated independently by 2 examiners. Observers used a strict definition of periapical disease and reported a positive finding (healing) only when absolutely certain. In Kvist 2000, postoperative discomfort was assessed by means of a questionnaire evaluating pain and swelling by VAS, analgesics intake and time off work resulting from participants' discomfort
Notes	Sample size calculation was performed before the start of the study (information provided by study author); in Kvist 2000, 88 questionnaires could be evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Cases were randomised to surgical or root canal retreatment by the "minimization method," as described by Pocock 1983. Three randomisation factors were considered: size of the periapical radiolucency, the apical position and technical quality of the root filling
Allocation concealment (selection bias)	Low risk	Closed envelopes were open soon before treatment (information provided by study author)
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was impossible to blind operators and participants to treatment (surgery vs non-surgery)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding to treatment was impossible for radiographic assessment; 2 examiners independently evaluated the radiographs
Incomplete outcome data (attrition bias) All outcomes	Low risk	87 of the 92 randomised participants were included in the 4-year analysis; reasons were provided for all dropouts
Selective reporting (reporting bias)	Low risk	All outcomes were adequately reported.

Kvist 1999 (*Continued*)

Other bias	Low risk	None was detected.

Lindeboom 2005a

Methods	Trial design: randomised, parallel-group trial Location: Amsterdam, The Netherlands Study centres: (affiliation) Department of Oral and Maxillofacial Surgery, Academic Medical Centre Amsterdam, University of Amsterdam, Amsterdam, The Netherlands Recruitment period: not specified ("over a period of 28 months") Source of funding: none declared Ethical approval: yes: medical ethical committee of the Academic Medical Centre of Amsterdam Number of surgeons: 2
Participants	Inclusion criteria: tooth with apical periodontitis with an adequate root filling and coronal restoration Exclusion criteria: teeth with perforations of the lateral canal walls, periodontal attachment loss (pocket depth > 5 mm), vertical fractures and teeth exhibiting radiographic lesions exceeding 1 cm. Patients with acute symptoms of endodontic infection such as submucosal swelling and erythema were also excluded from the study, as were patients who had received antibiotics before surgery. Other exclusion criteria were hypersensitivity for clindamycin, systemic disease and a medical condition that required prophylactic antibiotics. Age at baseline: average 44.4 ± 11.4 (range 18 to 82 years) (data also provided per group) Gender: W147/M109 (data also provided per group) Smokers: not reported Teeth treated: all types, detailed in a table (data also provided per group) Number randomised (participants/teeth): 256/256 Number evaluated (participants/teeth): 256/256 Size of lesion: ≤ 10 mm
Interventions	Comparison: prophylactic antibiotic administration vs placebo Test group: antibiotic (n = 128 participants/128 teeth) Control group: placebo (n = 128 participants/128 teeth) Surgical technique: root-end resection: root apex bevelled 10 to 25°; apical preparation performed with ultrasonic instruments; IRM used as root-end filler Follow-up duration: 4 weeks
Outcomes	Assessment of wound healing for signs of infection
Notes	Sample size calculation not performed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Lindeboom 2005a (*Continued*)

Random sequence generation (selection bias)	Low risk	Sealed envelopes with a study ID number were picked up by an assisting nurse before treatment administration
Allocation concealment (selection bias)	Low risk	Participants, oral and maxillofacial surgeons and investigators were blinded to random allocation throughout the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Envelopes contained a study-identification number with two capsules of placebo or clindamycin. Blind administration of study drugs was ensured through the use of labelled sets of identical looking tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Operators were blinded to group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the final analysis
Selective reporting (reporting bias)	Low risk	All outcomes were adequately reported.
Other bias	Unclear risk	Sample size calculation was missing, although the study population appears adequate; no details on smokers, recruitment dates and sources of funding were provided

Lindeboom 2005b

Methods	Trial design: randomised, parallel-group trial Location: Amsterdam, The Netherlands Study centres: Oral and Maxillofacial Surgery Department of the Academic Medical Center of Amsterdam Recruitment period: 1 July 2000 to December 2002 (info provided by study author) Source of funding: not funded; the department paid the costs (info provided by study author) Ethical approval: approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam (info provided by study author) Number of surgeons: 3 (info provided by study author)
Participants	Inclusion criteria: Patients had to undergo a surgical periapical endodontic procedure under local anaesthesia; tooth to be treated had a dental history of a root canal treatment and demonstrated a periradicular lesion of strictly endodontic origin with or without clinical signs or symptoms; only single-rooted teeth were included. Exclusion criteria: teeth with perforations of the lateral canal walls, periodontal attachment loss (pocket depth > 5 mm), teeth with vertical fractures, teeth exhibiting radiographic lesions exceeding 1 cm

Lindeboom 2005b (*Continued*)

	Age at baseline: average 43.4 ± 11.1 years (range 17 to 64 years) Gender: W57/M33 (2 teeth in 10 participants were treated - 8 female and 2 male) Smokers: not reported Teeth treated: anterior maxillary or mandibular teeth and maxillary and mandibular single-rooted premolars Number randomised (participants/teeth): 90/100 (In Methods, it is first stated that 100 consecutive patients were included, and is later stated that 57 female + 33 male = 90 patients, of whom 10 patients with two teeth were treated, each in separate surgical sessions; the unit of randomisation was the tooth (info provided by study author)) Number evaluated (participants/teeth): 90/100 Size of lesion: not exceeding 10 mm
Interventions	Comparison: MTA (mineral trioxide aggregate) vs IRM (intermediate restorative material) as root-end filling material Test group: MTA (n = 50 participants/50 teeth) Control group: IRM (n = 50 participants/50 teeth) Surgical technique: root-end resection: root apex bevelled 10 to 25°; apical preparation performed with ultrasonic instruments, visualised under surgical loupes Follow-up duration: 1 year
Outcomes	Clinical and radiographic healing
Notes	Interobserver agreement by kappa statistics was done and reported; sample size calculation was performed but was not presented in detail

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was done on a tooth basis (info provided by study author) "Randomization was carried out by a nurse who picked a sealed envelope and opened it at the time of placement of the retrograde filling." Consecutive participants were randomised. Study authors explained that in the 10 participants who had 2 teeth treated, the second tooth underwent independent randomisation and was treated in a separate surgical session
Allocation concealment (selection bias)	Low risk	The envelope was opened at the time of placement of the root-end filling. On a label, the name of the filling material was written

Lindeboom 2005b (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome of the healing process was evaluated by 2 independent assessors, who were not involved in the surgical procedure
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data were provided for all randomised participants.
Selective reporting (reporting bias)	Low risk	All outcomes were adequately reported.
Other bias	Low risk	Sample size calculation details were not clearly reported; no details on smokers were provided

Payer 2005

Methods	Trial design: randomised, parallel-group trial (3 arms) Location: Graz, Austria Study centres: Department for Oral Surgery and Radiology, Dental School, Medical University Graz Recruitment period: not reported Source of funding: not stated Ethical approval: not stated Number of surgeons: 4 oral surgeons
Participants	Inclusion criteria: healthy dental and periodontal status before and after surgery (Community Periodontal Index of Treatment Needs (CPITN) 0 to 2) Exclusion criteria: smokers of > 5 cigarettes/d Age at baseline: average 45 years (range 20 to 79 years) Gender: W38/M34 Smokers: 15/72 (all up to 5 cigarettes/d) (4 in test, 5 in placebo, 6 in control groups) Teeth treated: upper and lower incisors and premolars Number randomised (participants/teeth): 72/72 Number evaluated (participants/teeth): 72/72 Size of lesion: < 5 mm
Interventions	Comparison: low energy level laser therapy (LLLT) vs placebo vs control Test group: irradiation performed intraoperatively and postoperatively 1, 3 and 7 days after surgery (n = 24 participants/24 teeth) Placebo group: irradiation without laser activation (n = 28 participants/28 teeth) Control group: Neither LLLT nor placebo therapy was used (n = 20 participants/20 teeth) Surgical technique: Root-end resection was performed; the root tip was exposed with round burs, and a fissure bur was used for root resection; retrograde root canal preparation was accomplished with diamond-coated ultrasonic instruments (Piezon Master 400,

Payer 2005 (*Continued*)

	EMS GmbH, Munich, Germany) under apical magnification. The root-end filling was performed with IRM Follow-up duration: 7 days post surgery
Outcomes	Swelling, inflammation, bleeding, disturbance of sensitiveness, dehiscences, oral hygiene and pain. Pain was assessed by a visual analogue scale (VAS), a numerical rating scale (NRS) and a verbal rating scale (VRS)
Notes	Sample size calculation was not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details on the randomisation procedure ("patients were split randomly in the three groups") were provided
Allocation concealment (selection bias)	Unclear risk	It was not mentioned if allocation was concealed until treatment delivery. No reply was received from study authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants in the placebo group were not aware that the laser was not activated during irradiation. Control participants were informed of participating in a study on the outcome of endodontic surgery but did not know what treatment was given to the other 2 groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A separate completely blinded investigator evaluated the parameters at 1, 3, 7 days post-op; the statistician was not involved in the clinical nor the operative part of the study
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Four patients had to be excluded from the study for lack of oral hygiene after surgery," but it was not specified to which group(s) these participants belonged
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported, although for pain measured through NRS and VAS, only diagrams were provided, and it was not possible to obtain data for meta-analysis

Payer 2005 (*Continued*)

Other bias	Low risk	Sample size calculation was not reported; no details on recruitment period, source of funding or ethical approval were provided

Pecora 2001

Methods	Trial design: randomised, parallel-group trial Location: Rome, Italy Study centres: 1 centre (private practice, Rome) Recruitment period: not reported Source of funding: not reported Ethical approval: not stated Number of surgeons: 1 operator performed all surgeries; another operator prepared and placed the calcium sulphate
Participants	Inclusion criteria: previous root canal treatment and retreatment (except 2 cases) with persistence of a bony lesion; presence of a periapical bone defect > 10 mm with lack of both buccal and lingual plates diagnosed preoperatively by periapical radiographs, finger palpation and bone probing; all patients presented with fistula tracts and recurrent episodes of purulent discharge; all cases (except 2) received conventional root canal retreatment. After a minimum follow-up of 3 months, if the lesion had remained unchanged, the patient was scheduled for periradicular surgery and was included in the present study. Exclusion criteria: failure to satisfy inclusion criteria Age at baseline: average 48 years (range 30 to 60 years) Gender: not stated Smokers: none Teeth treated: not reported Number randomised (participants/teeth): 20/20 Number evaluated (participants/teeth): 18/18 (1 tooth per group had to be extracted) Size of lesion: > 10 mm
Interventions	Comparison: grafting with calcium sulphate vs no grafting Test group: grafting of the bone defect with calcium sulphate (Surgiplaster, Class Implant, Rome, Italy) (n = 10 participants/10 teeth) Control group: no grafting (n = 10 participants/10 teeth) Surgical technique: root-end resection; root-end filling with SuperEBA cement under magnification with a surgical microscope Follow-up duration: 12 months
Outcomes	Radiographic healing (according to the criteria provided by Rud 1972)
Notes	No sample size calculation was performed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Pecora 2001 (*Continued*)

Random sequence generation (selection bias)	Low risk	Cases were randomly assigned by flipping a coin.
Allocation concealment (selection bias)	Low risk	The coin was flipped before surgery. After performing the conventional surgical technique (i.e. apicoectomy and root-end filling), operators were given an envelope, which disclosed to which group the participant they were operating on belonged
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Two operators, both unaware of the group to which operating sites belonged, performed all surgeries
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The outcome of the healing process was radiologically evaluated by three independent examiners who were not involved in the surgical procedure and blind with respect to the test or control group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Other than the 2 participants who had to undergo extraction of the treated tooth, all randomised participants were included in the final analysis
Selective reporting (reporting bias)	Low risk	All outcomes were reported in detail.
Other bias	Unclear risk	Sample size calculation was missing; no details on recruitment dates, source of funding, ethical approval, gender, smokers or teeth treated were provided

Song 2012

Methods	Trial design: randomised, parallel-group trial Location: Seoul, Korea Study centres: Department of Conservative Dentistry at the Dental College, Yonsei University, Seoul, Korea Recruitment period: February 2003 to October 2010 Source of funding: not stated Ethical approval: obtained from the Yonsei University Committee for Research on Human Subjects Number of surgeons: 1
Participants	Inclusion criteria: All root-filled cases with symptomatic or asymptomatic apical periodontitis were included. Exclusion criteria: Teeth with class II or greater mobility, horizontal and vertical fractures

	and perforations were excluded from the study. Through endodontic microsurgery, teeth with a through-and-through lesion and/or a lesion of combined periodontal endodontic origin were also excluded. Age at baseline: presented only as frequencies per age range Gender: W69/M123 Smokers: not stated Teeth treated: 73 maxillary anterior, 31 maxillary premolar, 28 maxillary molar; 21 mandibular anterior, 11 mandibular premolar, 28 mandibular molar Number randomised (participants/teeth): 260/260 Number evaluated (participants/teeth): 192/192 Size of lesion: not stated
Interventions	Comparison: mineral trioxide aggregate (MTA) vs super ethoxy-benzoic acid (SuperEBA) Test group: MTA (participants/teeth): 90/90 Control group: SuperEBA (participants/teeth): 102/102 Surgical technique: root-end resection, With the exception of incisions, flap elevation and suturing, all surgical procedures were performed with an operating microscope. The root tip was sectioned with a tapered fissure bur under copious sterile distilled water irrigation. The root-end preparation was made with KIS ultrasonic tips driven by a Piezoelectric ultrasonic unit. The root-end filling material used was SuperEBA or ProRoot MTA, which was selected according to the randomisation Follow-up duration: 12 months
Outcomes	The primary outcome measure for this study was the change in apical bone density at 12 months. Radiographic findings, which were taken from 3 angles (straight and 20° mesial and distal), were evaluated blindly and independently by 2 examiners, who used the same criteria as those used by Molven 1987. Secondary outcome measures included the presence of clinical symptoms or abnormal findings at 12 months, such as any pain and/or swelling or loss of function, tenderness to percussion or palpation, subjective discomfort, mobility, sinus tract formation and periodontal pocket formation. Criteria for failure included any clinical signs and/or symptoms or radiographic evidence of uncertain or unsatisfactory healing
Notes	Sample size calculation was performed. The 2 examiners standardised the evaluation criteria before they performed case analyses, so that their results were based on the same evaluation methods and conditions. Cohen kappa statistical analysis was used to measure interexaminer variability

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Teeth were randomly assigned to groups by the Pocock "minimization method." The random allocation sequence was generated by an assistant. The following 3 randomisation factors were considered: sex, age and tooth type

Song 2012 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	This was not stated. We received no reply from study authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants was not clearly stated. Operators could not be blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Radiographs were evaluated blindly and independently by 2 examiners
Incomplete outcome data (attrition bias) All outcomes	High risk	The study had a 26% dropout at 1-year follow-up, which is rather high; in 63/68 cases, the reason was "fail to attend" with no attempt to explain why participants did not attend. All data were reported for all randomised participants completing the trial
Selective reporting (reporting bias)	Low risk	Outcomes were adequately reported.
Other bias	Unclear risk	No details on source of funding, smokers or lesion size were reported

Taschieri 2007

Methods	Trial design: randomised, parallel-group trial Location: Milano, Italy Study centres: Istituto Ortopedico Galeazzi, Department of Health Technologies, Dental Clinic, Università degli Studi di Milano, and private practice, Milano, Italy Recruitment period: 24 months (dates not specified) Source of funding: none (information provided by study author) Ethical approval: The study protocol was evaluated and approved by the Review Board of the University of Milano, Italy Number of surgeons: 2
Participants	Inclusion criteria: The tooth treated surgically showed a periradicular lesion of strictly endodontic origin, and root canal retreatment was considered unfeasible or had previously failed. The minimum diameter of the bone defect, as determined from periapical radiographs, was at least 10 mm. The tooth treated surgically exhibited adequate final restoration with no clinical evidence of coronal leakage. Patients had no general medical contraindications for oral surgical procedures (ASA-1 or ASA-2 rating). Exclusion criteria: teeth with any kind of pathoses associated with vertical root fracture, teeth with perforation of the furcation area or lateral canal walls; teeth with traumatic injury; severe periodontal bone loss detected with a periodontal probe (≥ 5 mm probing depth) Age at baseline: 36 years for women, 43 years for men Gender: W29/M15 (evaluated: W28/M13) Smokers: 10/44 participants were smokers of fewer than 15 cigarettes/d (information

	provided by study authors). Teeth treated: 2 participants (accounting for 3 teeth) did not return at follow-up; 1 tooth was extracted because of intraoperative root perforation; teeth evaluated at 1 year included 39 in the maxilla (16 anterior, 14 premolars, 9 molars) and 20 in the mandible (10 anterior, 6 premolars, 4 molars) Number randomised (participants/teeth): 44/63 Number evaluated (participants/teeth): 41/59 Size of lesion: ≥ 10 mm
Interventions	Comparison: GTR (bone grafting and resorbable membrane) vs no GTR for surgical treatment of large periapical lesions Test group (GTR group): grafting (anorganic bovine bone, Bio-Oss, Geistlich Pharma, Wolhusen, Switzerland) (participants/teeth) and resorbable collagen membrane (BioGide, Geistlich Pharma): 16/24 Control group: no grafting (participants/teeth): 25/35 Four-wall defects and through-and-through lesions were also compared Surgical technique: root-end resection. Surgical access to the root was attained through the cortical bone with a round bur. The periradicular lesion was removed with sharp bone curettes and angled periodontal curettes. After exposure of the root-end, a straight fissure bur in a handpiece was used to cut 2.5 to 3 mm of the root-end. Root-end cavities were prepared with zirconium nitrate retro-tips driven by an ultrasonic device unit. Zinc oxide EBA-reinforced cement was used as the root-end filling material. In cases allocated to the GTR group, the bone defect was filled with bovine bone mineral, then was covered with a resorbable collagen membrane. No grafting nor membrane was used in the control group Follow-up duration: 1 year
Outcomes	Radiographic healing according to Molven 1987 criteria
Notes	Sample size calculation was missing; the study was tooth-based - not participant-based

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Treatment was assigned through a computer-generated randomised table
Allocation concealment (selection bias)	High risk	This was not performed (information provided by study authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Surgeons could not be blinded to treatment, and participants were informed of the treatment received
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Two blinded examiners independently evaluated all radiographs at 4.3× magnification with the use of surgical magnification loupes

Taschieri 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Three participants could not be evaluated at follow-up (reasons were provided). All data were reported for all randomised participants completing the trial
Selective reporting (reporting bias)	Unclear risk	All outcomes were adequately reported, although on a tooth basis
Other bias	Low risk	Sample size calculation was not performed.

Taschieri 2008

Methods	Trial design: randomised, parallel-group trial with 3 arms Location: Milano, Italy Study centres: Istituto Ortopedico Galeazzi, Department of Health Technologies, Dental Clinic, Università degli Studi di Milano, and private practice, Milano, Italy Recruitment period: 22 months, from December 2001 to December 2004 Source of funding: none (information provided by study author) Ethical approval: Institutional Review Board of Galeazzi Orthopedic Institute, Milano, Italy (information provided by study author) Number of surgeons: 2
Participants	Inclusion criteria: A periradicular lesion of strictly endodontic origin was present; root canal retreatment was considered unfeasible or had previously failed; the tooth treated surgically exhibited an adequate final restoration with no clinical evidence of coronal leakage; the apical root canal had 6 mm or more without the presence of a post; acute symptoms were absent; patient had no general medical contraindications for oral surgical procedures (ASA-1 or ASA-2). Exclusion criteria: teeth with any kind of pathoses associated with vertical root fracture; teeth with perforation of the furcation area or lateral canal walls; teeth with traumatic injuries; molars; severe periodontal bone loss detected with a periodontal probe (≥ 5 mm probing depth); bone defect involving both buccal and lingual cortical bone Age at baseline: average 38 years for women and 41 years for men. In Taschieri 2008, mean age was 43 years (women) and 37 years (men) in the microscope group, and 41 years (women) and 40 years (men) in the endoscope group. Gender: W53/M45 Smokers: 18/98 participants were smokers of fewer than 15 cigarettes/d; 2 smoked more than 15 cigarettes/d (information provided by study authors). Teeth treated: 34 in maxilla and 37 in mandible; both single- and multi-rooted teeth; 45 anterior teeth and 21 premolars Number randomised (participants/teeth): 98/150 Number evaluated (participants/teeth): 85/132 Size of lesion: Maximum size ranged between 3 mm and 19 mm
Interventions	Comparison: magnification loupes vs endoscope in root-end management (Taschieri 2006); surgical microscope vs endoscope (Taschieri 2008) Test group: endoscope (Hopkins Tele-Otoscope 70°; Karl Storz GmbH) (patients/teeth) : 34/50

	Test group: microscope (patients/teeth): 36/63 Control group: magnification loupes (patients/teeth): 28/37 Surgical technique: Root-end resection was performed. Surgical access to the root was made through the cortical bone with a round bur. The periradicular lesion was removed with sharp bone curettes and angled periodontal curettes. After exposure of the root-end, a straight fissure bur in a handpiece was used to cut 2.5 to 3 mm of the root-end. All of these procedures were performed with magnification loupes (4.3×) with a headlight. After root-end resection, surgical procedures were performed with the same loupes or with an endoscope or a microscope. Root-end cavities were prepared with zirconium nitrate retro-tips driven by an ultrasonic device unit. Zinc oxide EBA-reinforced cement was used as the root-end filling material Follow-up duration: 24 months (Taschieri 2008)
Outcomes	Radiographic criteria established by Molven 1987 were used for outcome assessment: complete healing, incomplete healing, uncertain healing or unsatisfactory outcome. Clinically, any evidence of signs and/or symptoms was recorded, according to the guidelines of Gutmann 1991. All clinical records were supplied to the observers.
Notes	Sample size calculation was performed before enrolment. To reduce the effect of evaluator fatigue as a confounding variable, 10 radiographs were viewed consecutively; then a 15-minute break was taken before the next evaluation session

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer-generated randomised table was used; the participant - not the tooth - was randomised
Allocation concealment (selection bias)	Low risk	A closed, opaque envelope containing the indication for which the magnification device was to be used was opened before the start of each surgical operation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were blinded, and the operator could not be blinded to magnificator type
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Two blinded examiners independently evaluated radiographs at 4.3× magnification with magnification loupes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Thirteen participants (18 teeth) could not be evaluated at follow-up (reasons were provided). All data were reported for all randomised participants completing the trial

Taschieri 2008 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	All outcomes were adequately reported, although on a tooth basis
Other bias	Low risk	None was detected.

Velvart 2004

Methods	Trial design: randomised, split-mouth trial Location: Zurich, Switzerland Study centres: University of Basel, University of Geneva, Switzerland Recruitment period: not stated Source of funding: not stated Ethical approval: not stated Number of surgeons: not specified (probably 2)
Participants	Inclusion criteria: root-filled teeth failing with persisting symptoms and/or apical radiolucency; conventional retreatment failed or unfeasible; no signs of periodontal disease (absence of bleeding on probing, no more than 3 mm probing depth in involved teeth) ; interdental papillae occupying the interproximal space below the contact area Exclusion criteria: failure to satisfy entry criteria Age at baseline: average 45 ± 9.4 years (range 36 to 63 years) Gender: W6/M6 Smokers: not stated Teeth treated: 6 anterior teeth, 4 premolars, 3 molars (both jaws) Number randomised (participants/teeth): 12/12 Number evaluated (participants/teeth): 12/12 Size of lesion: not stated
Interventions	Comparison: papilla base incision (PBI) vs complete papilla mobilisation Test group: complete base incision (n = 12 participants/12 teeth) Control group: standard papilla mobilisation (n = 12 participants/12 teeth) Surgical technique: Root-end resection was performed. The entire surgical procedure was performed with microsurgical instruments and magnified vision of at least 4.3× with loupes and an operating microscope. Only details of the incision/flaps are reported; no details of the apical surgery procedure are provided Follow-up duration: 12 months
Outcomes	Height of interdental papilla with plaster replicas and laser scanner
Notes	Sample size calculation was not reported. No details about smokers, lesion size, source of funding, recruitment period, ethical approval or number of surgeons were given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Velvart 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Randomisation method was not specified. The paper reports: "The incision technique applied to the mesial or distal interproximal space was randomly selected."
Allocation concealment (selection bias)	High risk	Allocation concealment was not applicable in this split-mouth study
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was impossible to blind the operator.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No assessor blinding was reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data were reported for all randomised participants.
Selective reporting (reporting bias)	Low risk	All outcomes were adequately reported.
Other bias	High risk	Sample size calculation was missing.No details about smokers, lesion size, source of funding, recruitment period, ethical approval or number of surgeons were given

Walivaara 2009

Methods	Trial design: randomised, parallel-group trial Location: Halmstad, Sweden Study centres: Maxillofacial Unit, Halmstad Hospital, Sweden Recruitment period: not specified Source of funding: not stated Ethical approval: not stated Number of surgeons: 2
Participants	Inclusion criteria: all referred patients for periapical surgery living a maximum of 40 kilometres from the hospital Exclusion criteria: advanced periodontal disease with apical marginal communications and obvious root fractures Age at baseline: average 58.5 years Gender: W81/M58 Smokers: not stated Teeth treated: 46 incisors, 10 canines, 42 premolars, 49 molars Number randomised (participants/teeth): 139/160 Number evaluated (participants/teeth): 131/147 Size of lesion: not stated

Interventions	Comparison: ultrafill thermoplasticised gutta-percha vs IRM as root-end fillings Test group: IRM (n = 68 participants/X teeth): 77 teeth Control group: ultrafill thermoplasticised gutta-percha (n = 71 participants/X teeth): 83 teeth Surgical technique: Root-end resection was performed with 2.3x magnification operating loupes. The bony periapical area was exposed with a round bur. Enucleation of the granuloma or cyst was followed by a slightly oblique resection of the root with a fissure bur. The root canal was prepared and cleaned with ultrasonic root-end cavity preparation Follow-up duration: 12 to 38 months, average 15.6 months
Outcomes	The clinical evaluation was performed by 1 of 5 independent surgeons. Molven 1987 and Rud 1972 criteria were adopted. Any clinical findings such as tenderness on percussion, tenderness on palpation on the crown and/or in the apical area, gingival swelling and presence of fistula or apicomarginal communication were registered as a failure
Notes	Sample size calculation was not reported. No details about smokers, lesion size, source of funding, recruitment period or ethical approval were given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Participants were randomly allocated to 2 groups according to date of birth
Allocation concealment (selection bias)	High risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants was not clearly stated. Operators could not be blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Radiographic assessment was made by 3 independent operators (2 operating surgeons and a maxillofacial radiologist), but no blinding to treatment was mentioned. Before the assessment, all met to calibrate for a consensus
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Eight participants (13 teeth) could not be evaluated (reasons were provided). For all other randomised participants, only tooth-based data were provided
Selective reporting (reporting bias)	Unclear risk	Outcomes on success and failure were reported in detail, although only on a tooth basis; data per participant were not reported

Other bias	High risk	Sample size calculation was missing. No details about smokers, lesion size, source of funding, recruitment period or ethical approval were given. Follow-up was not the same for all participants

Walivaara 2011

Methods	Trial design: randomised, parallel-group trial Location: Halmstad, Sweden Study centres: Maxillofacial Unit, Halmstad Hospital, Sweden Recruitment period: September 2006 to December 2008 Source of funding: not stated Ethical approval: yes, approved by the human ethical committee at the University of Lund, Sweden Number of surgeons: 2
Participants	Inclusion criteria: consecutive patients referred to the department for an apical surgery procedure on all types of teeth Exclusion criteria: teeth with obvious root fracture or advanced periodontal disease Age at baseline: not stated Gender: W99/M65 Smokers: not stated Teeth treated: 40 incisors, 16 canines, 57 premolars and 81 molars in both jaws Number randomised (participants/teeth): 164/206 Number evaluated (participants/teeth):153/194 Size of lesion: Distribution of lesion size and lesion type amongst the 194 followed teeth was reported in a table
Interventions	Comparison: 2 different root-end filling materials: IRM vs SuperEBA Test group: IRM (participants/teeth): not specified/96 teeth Control group: SuperEBA (participants/teeth): not specified/98 teeth Surgical technique: Root-end resection was performed with 2.3x magnification operating loupes. The bony periapical area was exposed with a round bur. The root canal was prepared and cleaned with ultrasonic root-end cavity preparation Follow-up duration: range 12 to 21 months, average 13.1 months
Outcomes	Registration of clinical findings such as tenderness on percussion, tenderness on palpation of the crown and/or in the apical area, gingival swelling and presence of a fistula or an apicomarginal communication was recorded as a failure. Clinical and radiographic healing was assessed according to the Molven 1987 and Rud 1972 criteria.
Notes	Sample size calculation was not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Walivaara 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	A standard randomisation table was used.
Allocation concealment (selection bias)	High risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants was not clearly stated. Operators could not be blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinical and radiographic assessment was made by independent operators (2 operating surgeons and a maxillofacial radiologist), but no blinding to treatment was mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Eleven participants (12 teeth) could not be evaluated (reasons were provided). For all other randomised participants, only tooth-based data were provided
Selective reporting (reporting bias)	Unclear risk	Outcomes on success and failure were reported in detail, although only on a tooth basis; data per participant were not reported
Other bias	High risk	Sample size calculation was missing; no details on source of funding, participants' age at baseline or smokers were provided. Follow-up was not the same for all participants

Zetterqvist 1991

Methods	Trial design: randomised, parallel-group trial Location: Stockholm, Sweden Study centres: Department of Oral Surgery, Karolinska Institute, Stockholm Recruitment period: not stated Source of funding: not stated Ethical approval: The study was approved by the local ethical committee of Huddinge Hospital (information taken from Jesslen 1995) Number of surgeons: 2
Participants	Inclusion criteria: presence of teeth with periapical lesions not accessible to conventional endodontic treatment Exclusion criteria: not stated Age at baseline: not stated Gender: not stated Smokers: not stated Teeth treated: not stated

Zetterqvist 1991 (*Continued*)

	Number randomised (participants/teeth): 85/105 Number evaluated (participants/teeth): 85/105 (67/82 in Jesslen 1995) Size of lesion: not stated
Interventions	Comparison: glass ionomer cement (GC) vs amalgam Test group: glass ionomer cement (53 teeth) Control group: amalgam (52 teeth) Surgical technique: Root-end resection was performed. Any bone covering the apical area and any granulation tissue were removed. Apicoectomy was performed, and the root canal was prepared in a box-type manner with an inverted cone bur. Each tooth was filled with amalgam or GC Follow-up duration: 1 year; 5 years (Jesslen 1995)
Outcomes	Clinical and radiographic healing. Standardised radiographs were obtained and interpreted by one of the study authors trained in oral radiology. The following 4 classifications were used: complete healing, improvement, no improvement, failure
Notes	Sample size calculation was not reported; participant dropout was 21.2% at 5 years (Jesslen 1995). Periapical healing was assessed by personal criteria instead of conventional criteria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Treatment was allocated "in accordance with a randomisation form."
Allocation concealment (selection bias)	High risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not stated.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The investigator was aware of the treatment that each participant had received because GC shows no radiographic contrast; at 5 years, the 2 investigators were not independent (Jesslen 1995)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants were seen at 1-year follow-up, and all outcomes were reported; 18 participants (23 teeth) could not be included in the 5-year follow-up and were considered dropouts (21% participants) (Jesslen 1995)
Selective reporting (reporting bias)	Unclear risk	Healing data were provided on a tooth basis only.

Zetterqvist 1991 (*Continued*)

Other bias	High risk	No sample size calculation was reported; no details of participant demographics (age, gender, smokers), tooth type, lesion size, source of funding, recruitment period or exact numbers of participants allocated to test and control groups were given. Personal criteria instead of conventional criteria were used in evaluating periapical healing

ASA: American Society of Anesthesiologists.
CBCT: cone beam computed tomography.
CPITN: Community Periodontal Index of Treatment Needs.
GC: glass ionomer cement.
GTR: bone grafting and resorbable membrane.
IRM: intermediate restorative material.
MTA: mineral trioxide aggregate.
NRS: numerical rating scale.
PAI: periapical index.
PBI: papilla base incision.
PRF: platelet-rich fibrin.
PRGF: plasma rich in growth factors.
SI: sulcular incision.
VAS: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bader 1998	Participants were not actually randomised to treatment.
Dhiman 2015	This study examined apicomarginal defects (in the present review, only lesions confined to the periapical region were to be considered)
Garrett 2002	Recruitment was defective, and the dropout rate was extremely high. Of the 60 participants planned to be recruited according to the sample size calculation, only 25 were indeed treated and, of these, only 13 were evaluated at the scheduled follow-up
Goyal 2011	This study examined apicomarginal defects (in the present review, only lesions confined to the periapical region were to be considered)
Huumonen 2003	This was not a study on endodontic surgery. Researchers evaluated only orthograde retreatment

(*Continued*)

Kim 2008	This study on endodontic microsurgery compared a group with apical lesions and a group with apicomarginal defects (in the present review, only lesions confined to the periapical region were to be considered)
Marin-Botero 2006	This study examined apicomarginal defects (in the present review, only lesions confined to the periapical region were to be considered)
Shearer 2009	Follow-up for this study was too short (6 months).
Von Arx 2010a	Participants were not actually randomised to treatment.

DATA AND ANALYSES

Comparison 1. Root-end resection versus root canal retreatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing - 1 year	2	126	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.97, 1.35]
2 Healing - 4 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Healing - 10 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Participants reporting pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 day 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 day 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 day 4	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 day 5	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 day 6	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Participants reporting swelling	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 day 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 day 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 day 4	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.5 day 5	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.6 day 6	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.7 day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. CBCT versus periapical radiography

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing - 1 year	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Antibiotic prophylaxis versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Occurrence of postoperative infection - 4 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Magnification devices

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Loupes versus endoscope - healing at 1 year	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Microscope versus endoscope - healing at 2 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Type of incision

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PBI versus complete mobilisation - papilla height	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2 PBI versus complete mobilisation - pain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 1 day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 2 days	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 3 days	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Ultrasonic versus bur

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing - 1 year	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 7. Root-end filling material

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MTA versus IRM - healing at 1 year	2	222	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.97, 1.22]
2 MTA versus IRM - healing at 2 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 MTA versus IRM - pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 1 day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 2 days	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

4 SuperEBA versus MTA - healing at 1 year	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 MTA versus gutta-percha - healing at 1 year	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 MTA versus gutta-percha - pain	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 1 day	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 2 days	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 3 days	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Glass ionomer cement (GIC) vs amalgam - healing at 1 year	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Glass ionomer cement (GIC) vs amalgam - healing at 5 years	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 IRM vs Gutta-percha - healing > 1 year	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 IRM vs SuperEBA - healing > 1 year	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 8. Grafting versus no grafting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Calcium sulphate (CaS) versus no grafting - healing at 1 year	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 GTR with bovine bone vs no grafting - healing at 1 year - TB	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 PRGF versus no grafting - pain (VAS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 1 day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 2 days	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 3 days	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 9. Low energy level laser therapy (LLLT) versus placebo versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum pain (VRS)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 LLLT vs control	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 LLLT vs placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 placebo vs control	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

WHAT'S NEW

Last assessed as up-to-date: 10 February 2016.

Date	Event	Description
7 December 2016	Amended	Minor correction: magnification devices were not used in the De Lange 2007 study. The reference to a microscope having been used in the ultrasonic group has been corrected in the 'Other potential risks of bias' section and the relevant 'Characteristics of included studies' table. Risk of bias and quality assessments are unaffected

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 3, 2007

Date	Event	Description
16 August 2016	New citation required and conclusions have changed	Evidence for root-end resection versus root canal retreatment is inconclusive This update includes evidence from eight comparisons of different aspects of the root-end section procedure: cone beam computed tomography versus periapical radiography for preoperative assessment; antibiotic prophylaxis versus placebo; different magnification devices; different types of incision; ultrasonic devices versus handpiece burs; different types of root-end filling material; grafting versus no grafting; low energy level laser therapy versus placebo versus control (no use of the laser device)
10 February 2016	New search has been performed	Review has been expanded to include comparisons of different surgical approaches to retreatment of periapical lesions. Title has been changed. New search was conducted. 17 new studies have been included. Unpublished data on longer-term follow-up were received from 1 trial author
31 July 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: Silvio Taschieri (ST), Massimo Del Fabbro (MDF).

Designing and co-ordinating the review: MDF.

Developing search strategies and undertaking searches: Stefano Corbella (SC), Eyal Rosen (ER).

Screening search results and retrieved papers against inclusion criteria: SC, MDF.

Writing to study authors for additional information: MDF, SC.

Appraising the quality of papers: Igor Tsesis (IT), Alessandra Lolato (AL), Patrick Sequeira-Byron (PSB).

Extracting data from papers: SC, AL, IT.

Screening data on unpublished studies: SC, IT.

Analysing data: SC, PSB, MDF.

Interpreting data: MDF, ST, ER.

Writing the review: MDF, SC.

Providing general advice on the review: ST, ER, IT.

Addressing referee comments: MDF, SC, PSB, AL.

DECLARATIONS OF INTEREST

The review authors declare that they are free from any commercial conflict of interest. Massimo Del Fabbro and Silvio Taschieri are investigators on studies included in the review; therefore, they were not involved in any assessment regarding those studies (quality appraisal, data extraction, analysis, interpretation).

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- Cochrane Oral Health Global Alliance, Other.

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- School of Dentistry, The University of Manchester, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title to reflect the change in scope.

We added a few sentences in the Background section, at the beginning of 'Description of the condition' and 'Description of the intervention', to better explain the aim of root canal therapy and the main differences between orthograde and surgical endodontic retreatment.

We included patient-reported outcomes such as postoperative pain and discomfort, as well as the follow-up time for such outcomes (first week after surgery).

We added the method of analysing studies with paired data (trials with split-mouth design) (generic inverse variance) in the 'Data synthesis' section.

Some review authors (MDF, ST) were among the authors of some of the included studies; therefore, only those review authors not involved in the trials (IT, PSB) performed the risk of bias assessment for these studies.

We included some parallel-group studies presenting data only on a tooth basis because the review authors agreed that these results were worth reporting, and we undertook meta-analysis if only tooth-based data, instead of patient-based data, were available for all studies addressing a given comparison. In split-mouth studies, the tooth was considered as the unit of analysis.

We dichotomised data regarding healing of the periapical lesion, which usually are expressed in four scores (complete, incomplete, uncertain, unsatisfactory healing), into 'healing' (complete plus incomplete healing data) and 'failure' (uncertain plus unsatisfactory healing data). In our previous version, we had included 'uncertain' results under 'healing'. For outcomes reported as continuous variables (e.g. pain, as expressed with VAS), we calculated the estimates of effects of interventions as mean differences (MDs).

INDEX TERMS

Medical Subject Headings (MeSH)

Periapical Periodontitis [surgery; *therapy]; Randomized Controlled Trials as Topic; Retreatment; Root Canal Therapy [*methods]

MeSH check words

Humans